Institute of Biomedical Ethics and History of Medicine, University of Zurich
Director: Prof. Dr. med. Dr. phil. Nikola Biller-Andorno

Dissertation under the supervision of Prof. Dr. med. Dr. phil. Nikola Biller-Andorno and Prof. Dr. phil. Marcel Tanner

Ethical Implications of Malaria Vaccine Development

INAUGURAL-DISSERTATION
To receive the title of (Dr. sc. med./PhD)
awarded by the Faculty of Medicine
University of Zurich

submitted by
Machteld van den Berg

Dissertation committee:
Prof. Dr. med. Dr. phil. Nikola Biller-Andorno (chair and main supervisor)
Prof. Dr. phil. Marcel Tanner (co-supervisor)
PD Dr. med. et sc. nat. Sonja Merten

This dissertation has been accepted by the Medical Faculty, University of Zurich
upon request of Prof. Dr. Dr. Nikola Biller- Andorno
Zurich 2019

Publication record

These dissertation chapters have been published/submitted in/to the following journals:

1. *RTS,S malaria vaccine pilot studies: addressing the human realities in large-scale clinical trials*

Machteld van den Berg, Bernhards Ogutu, Nelson Sewankambo, Nikola Biller-Andorno, Marcel Tanner

Published: May 2019

Journal: BMC Trials

2. *Clinical trials in low-resource settings: the perspectives of caregivers of paediatric participants from Uganda, Tanzania and Kenya*

Machteld van den Berg, Bernhards Ogutu, Nelson Sewankambo, Sonja Merten, Nikola Biller-Andorno, Marcel Tanner

Published: June 2019

Journal: Tropical Medicine & International Health

3. *Applying complexity theory to model the operation of clinical trials in human communities*

Machteld van den Berg, Bernhards Ogutu, Nelson Sewankambo, Sonja Merten, Nikola Biller-Andorno, Marcel Tanner

Submission date: March 2019

Journal: BMC Trials

4. *Communities and clinical trials: A case study from the RTS,S malaria vaccine trials in eastern Africa*

Machteld van den Berg, Bernhards Ogutu, Nelson Sewankambo, Sonja Merten, Nikola Biller-Andorno, Marcel Tanner

Submission date: August 2019

Journal: Journal of Empirical Research on Human Research Ethics

to my first teachers,

my mother and father

and their classroom,

the vegetable garden

a prairie field

or a buzzing beehive.

ABSTRACT

Clinical trials conducted in low-resource settings have unique challenges associated with their conduct. This is mainly attributed to the power and resource discrepancy between actors in the clinical trial. This thesis provides an in-depth look at clinical trials in low-resource settings and the effects of the resource discrepancy on the actors. It aims to answer what the ethical challenges are when conducting research in low-resource settings and the subsequent implications for research design. It focuses on capturing both the experience of caregivers of pediatric participants and the frontline researchers in a malaria vaccine clinical trial. Through exploring these two stories and bridging the relational with the formal, it provides a novel approach to address the challenges with research in low-resource settings. This approach employs the lens of complexity theory to evaluate the outcome of two systems, a human community and a clinical trial, merging.

I will begin by outlining a general introduction of clinical trials in low-resource settings and the case study of a pediatric malaria vaccine clinical trial, here I detail the need to generate a vaccine against malaria and outline why such research should take place. This situates the reasons for the study and provides familiarity with the contextual reality. Then I will move into detailing the caregiver experiences, researcher experiences, and the application of complexity theory to bridge together the different experiences.

This thesis is a result of qualitative data gathered from 78 interviews with caregivers of pediatric participants and 11 interviews with researchers involved on the frontline of a pediatric malaria vaccine clinical trial. The final part of the thesis is a theoretical reflection that explores the realities faced by researchers and argues for an approach that embraces the non-linearity of research taking place in human communities. Here I identify the challenges associated with choice and structural inequity, the conflict between beneficence and autonomy, and being a frontline researcher in low-resource settings.

ACKNOWLEDGEMENTS

Embarking on this PhD project together with the Institute of Biomedical Ethics and Law and the Swiss Tropical and Public Health Institute has been a wonderful experience for me as an early researcher. So, to start out, thank you to Nikola at the IBME who accepted me into the program and supervised my PhD, I am grateful for this opportunity you have given me and have appreciated your academic insight. And to Marcel at the Swiss TPH, your guidance, inspiration, and care has carried me through this PhD journey. My gratitude to you extends far beyond words that fit on this page – a deep thank you for all that you do for the students who are fortunate enough to be guided by you.

Thank you to all those who made this project possible. In particular the community respondents and members of the research team in Uganda, Kenya and Tanzania: your open arms and bravery in sharing your experiences has been one of my life's greatest honours. The local coordination and language support from many allowed for this project to become a reality. In particular, Sally Mtenga (Tanzania), Bernhards Ogutu (Kenya), Nelson Sewankambo (Uganda) for your help with the organisation and design of this project. And to the local research assistants who translated, interviewed and helped me connect to local communities – this would not have been possible without you. Thank you to Sonja for the qualitative expertise, your patient and reflective demeanor built a foundation in me as a social scientist. The administrative support I have received has been wonderful. Therefore, thank you to Daniela, Michelle and Dominik at the IBME and Margrith at the Swiss TPH for your help and vital role in project organisation.

To all my dear colleagues and friends: thank you! In particular, Manya and Martina, two fiercely bright women who have lit up my PhD journey in every which way. Your friendship runs deep, and you are two great blessings to come out of this experience. And also: Mirriam, Ana, Sebastian, Daniel, Corine, Holger and Matthias for the warmth and encouragement you have brought to our shared workplace.

To my first bioethics professor eight years ago, Doris, who continues to walk this journey with me as a dear friend – I would not be here without your support. Then my friends from across the globe, particularly in Canada, the list is too long and my words too vacant, but you have played

such a unique role in my life. My friends in Switzerland: Hannah, Julia, Silvan, Sandra, Nici, Jeanine, and Kevin you each make this country feel very much like home. My dear, dear Christian, your love has strengthened me for many years and has been my great cornerstone for this journey. From your small notes of encouragement to our long runs and garden projects, every step with you is the stuff of magic.

Most profoundly, thank you to my family where my roots are forever strong and protected. You have taught me, challenged me, and always nurtured me. My parents, Leen and Maria, thank you for being the embodiment of integrity and love. My siblings, Daniel, Josine and Leendert who keep me on my toes and ground me: it is not an understatement to say I would not be who I am without you.

And lastly, to all those not mentioned but who have inspired, loved and sustained me throughout my life. Thank you!

FUNDING

This work was supported by a Doc.CH grant from the Swiss National Science Foundation (SNSF P0ZHP1_172115), the Rudolf Geigy Foundation and the Canadian International Development Research Centre (IDRC).

TABLE OF CONTENTS

ABSTRACT **1**

ACKNOWLEDGEMENTS **3**

FUNDING **5**

TABLE OF CONTENTS **7**

ABBREVIATIONS **11**

INTRODUCTION **13**

Background **15**
Clinical trials in low-resource settings 15
A pediatric malaria vaccine as a case study 15
Why a malaria vaccine? 16

Malaria vaccine ethics **18**
Principle-based research ethics 18
Respect for autonomy 18
Beneficence and non-maleficence 20
Justice 21
Relational ethics 22

The broader picture **24**
The case study and clinical trials in low-resource settings 24
Research objectives 24

RTS,S MALARIA VACCINE PILOT STUDIES: ADDRESSING THE HUMAN REALITIES IN LARGE-SCALE CLINICAL TRIALS **27**

Abstract **29**

Introduction **31**

The role of relationship in research studies **33**

Communities and vaccine uptake **35**

Long-term monitoring of study sites **36**

Conclusions **37**

CLINICAL TRIALS IN LOW-RESOURCE SETTINGS: THE PERSPECTIVES OF CAREGIVERS OF PAEDIATRIC PARTICIPANTS FROM UGANDA, TANZANIA AND KENYA **41**

Abstract **43**

Introduction **45**

Methods **47**
Sample population 47
Trial 47
Study design 47
Ethics 48
Analysis 48

Results **49**
Trial Context 51
Community Context 52
Domestic Context 53

Discussion **55**

Conclusion **57**

APPLYING COMPLEXITY THEORY TO MODEL THE OPERATION OF CLINICAL TRIALS IN HUMAN COMMUNITIES **61**

Abstract **63**

Background **65**

Methods **67**
Study Design 67
In-depth interviews 67
Data analysis 68
Ethics 68

Results **69**
Communities are complex adaptive systems 69
Challenges of working in CAS 70
How researchers work in complex adaptive systems 72

Discussion **77**

Conclusion **82**

COMMUNITIES AND CLINICAL TRIALS: A CASE STUDY FROM THE RTS,S MALARIA VACCINE TRIALS IN EASTERN AFRICA **87**

Abstract **89**

Introduction **91**
Complexity Theory and Clinical Trials 92
Case Study: RTS,S Malaria Vaccine Phase III Clinical Trial 94

Methods **95**
Study Design 95
In-depth Interviews 95

Data Analysis 95
Ethics 96

Results 97
Blood draws 98
Benefits 99
Influencers and gatekeepers 99
Relationships 100
Finances 101
Communication 102
Health 103
Simple Rules 104

Discussion and Relevance 106

Conclusion 109

GENERAL DISCUSSION 111

Overview 113

Consent and choice 115
Should we do research when choice is diminished? 116
A conflict of principles 118
How to address diminished choice? 121

Researcher's embodied reality 127
Moral distress 127
The duty to rescue 128

Relational ethics 130
Strengthening agency 130
Trust 131
Roles and Responsibilities 135

CONCLUSION 139

Project Limitations 142
Implications for Future Research 143

REFERENCES 145

APPENDICES 163

Informed consent form caregivers 165
Caregiver interview guide 171
Informed consent form researchers 174
Researcher interview guide 180
Curriculum Vitae 183

ABBREVIATIONS

CAS	Complex Adaptive Systems
CAB	Community Advisory Board
CIOMS	Council for International Organizations guidelines
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IRBs	Institutional Review Boards
PMVT	Pediatric Malaria Vaccine Clinical Trial
RECs	Research Ethics Committees
SOPs	Standard Operating Procedures
SU-IRB	Strathmore University IRB

INTRODUCTION

BACKGROUND

Clinical trials in low-resource settings

The establishment of the Nuremburg code in 1948 stating that "The voluntary consent of the human subject is absolutely essential" formalized research ethics and advocated for informed consent and balanced risks and benefits in medical research. This first international document paved the way for subsequent recommendations - notably the Declaration of Helsinki, the Belmont Report, the Council for International Organizations guidelines (CIOMS) – as well as various other national and institutional ethics standards that provide guidance on medical research today (Council for International Organizations of Medical Sciences & World Health Organization, 2002; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978; World Medical Association, 2013). Despite the existence of these foundational documents, context-dependent ethical challenges continue to arise. Clinical trials in low-resource contexts have unique ethical challenges associated with their conduct due to the inequity of power and resources. When a clinical trial is launched in a low-resource setting, involving local communities, specific ethical challenges can be intensified by the inequity between actors. In this project I will investigate these ethical implications through a case study using a pediatric malaria vaccine trial (PMVT).

A pediatric malaria vaccine as a case study

I have chosen to use the RTS,S malaria vaccine phase III clinical trial as a case study for this project as it was a transnational trial, conducted across health and social systems (RTS,S Clinical Trials Partnership, 2015a). Due to the size and length of the trial it is particularly suited to studying the experiences of different actors in the clinical trial and the accompanying ethical implications. In the next part I will spend some time describing the PMVT by introducing the disease context, vaccine aims and development process to highlight the human realities in research such as the RTS,S phase III clinical trial.

Why a malaria vaccine?

In 2017 malaria was attributed to 435 000 deaths and nearly half the world's population was identified to be at risk of infection. Malarial disease carries an immense public health burden, and those at the highest risk for malaria are children living in endemic regions; it is estimated that 266 000 children died from infection in 2017 (WHO, 2018b). There are many intervention methods available, such as insecticide-treated bed nets, vector control and anti-malarial therapy, but those are not likely to lead to the rapid elimination of the disease (Rowe et al., 2007). In order to achieve the reduction of malaria incidence by 90% as outlined in Global Technical Strategy for Malaria 2016-2030, more tools are needed, including effective vaccines, especially in high transmission areas such as sub-Saharan Africa (World Health Organization, World Health Organization, & Global Malaria Programme, 2015). Today there is cautious optimism for a modestly effective vaccine called RTS,S developed in partnership by PATH Malaria Vaccine Initiate (MVI) and GlaxoSmithKline (GSK).

Due to the high burden of disease, a vaccine with a modest level of protection would translate into a significant impact given almost half a million annual deaths. Based on phase III studies that were carried out with RTS,S in conjunction with intervention methods, severe malaria cases were cut by one third (RTS,S Clinical Trials Partnership, 2015a). RTS,S has been shown to be most effective in children aged 5-17 months, who receive three doses of the vaccine and then a booster at 20 months of age, reducing the cases of severe malaria by 36% (Agnandji et al., 2012). In October of 2015 the WHO approved pilot testing of RTS,S for children in this age group (WHO, 2017b).

For immunological reasons it is very difficult to create an effective vaccine for malaria and RTS,S is at least 10 years ahead of all other vaccine candidates (Ballou, 2009). It targets the pre-erythrocytic state of *Plasmodium falciparum*, the malaria parasite with the highest burden of severe disease, by training the host's immune system to detect the parasite in the sporozoite stage –

triggering an immune response before infection of the liver or red blood cells (Sauboin, Bellinghen, Velde, & Vlaenderen, 2015). The vexing burden of malaria mortality and morbidity can silence ethical concerns that surround a modestly effective vaccine, yet previous well-intended elimination attempts have taught us to carefully consider the long-term consequences of such an endeavor (Byass, 2008; Ceesay et al., 2008; O'Meara et al., 2008).

Prosaic challenges common to vaccination in developing countries are also faced by RTS,S. It requires refrigeration, a particular problem in rural areas, and adds two medical visits to the routine vaccination schedule. Cold-chain management, preventing donor fatigue, and a feasible vaccination schedule are obstacles that require further clarification (Graboyes, 2015; Gulland, 2015). In addition to these pragmatic concerns, questions unique to malaria arise, such as how long the vaccine provides protection and if it reduces mortality or merely delays it. Malaria has co-evolved with humans for over 100 000 years and we have developed various traits to favour survival. Among these is acquired immunity, which develops in the first five years of life, the period of time where malaria carries the highest mortality rates. RTS,S targets this age group specifically to reduce the mortality, but potentially jeopardizing the acquisition of acquired immunity as a consequence. This has the potential to shift malaria epidemiology from a stable to an unstable form, rendering older individuals more susceptible or simply shifting mortality rates.

The outlined challenges are not insurmountable but do call for vigilant researchers committed to long-term monitoring of the vaccine research sites. Clear commitments to community involvement and publicly stated research goals will contribute to this process. To best support local researchers in this endeavor we need a better understanding of the local experiences and the accompanying ethical challenges. That is the aim of the empirical research conducted in this project, outlined in paper two, three and four. Before we explore that, we first need to position RTS,S in relation to the principles which lay the ethical foundation for clinical trial conduct. Next, we will outline these and systematically delineate some early questions relevant to these principles.

Principle-based research ethics

The Belmont report from 1979 acknowledged four foundational principles for research ethics: respect for autonomy, beneficence, non-maleficence, and justice (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). These principals are the foundation of biomedical ethics and lay the groundwork for ethical research (T. L. Beauchamp & Childress, 2009).

Respect for autonomy

Respect for autonomy ensures that individuals are able to make informed decisions voluntarily about participation in research studies. Obtaining informed consent is often singled out as the principle on which ethical research hinges, but empirical research shows that it is often not done as it should (Emanuel, Wendler, Killen, & Grady, 2004). Differences in language, social traditions, and practices complicate obtaining informed consent in regions such as sub-Saharan Africa (Fadare, Ademowo, & others, 2010). It is a process and must be carried out as such, yet has increasingly grown into a means to an end – with the focus on forms and processes – as opposed to securing informed, understanding and voluntary participation (Graboyes, 2015). The

foundations to ensure respect for autonomy in the sub-Saharan region are laid by the Declaration of Helsinki (World Medical Association, 2013) and CIOMS guidelines (Council for International Organizations of Medical Sciences & World Health Organization, 2002). However, this should also be viewed through the prism of RTS,S realities which includes pediatric subjects, collective societies and developing world contexts.

A challenge encompassing the voluntary nature of consent in RTS,S research is the vulnerable pediatric population it targets. Minors are unable to provide legal consent and parents are called upon to provide it on their behalf, many of whom may have a limited understanding of the terms informed consent and confidentiality (Kulkarni, 2013). Recent ethical guidelines have proposed a coupling of parental consent with participant's 'assent' to protect the young population enrolled; a potential tool for older participants (Council of Europe, 2007; Fadare et al., 2010). By exhibiting sensitivity to the local context and utilizing local language, culturally appropriate idioms, and analogies that are commonly used in the local culture these confounding factors can be minimized (Kithinji & Kass, 2010).

Within the collective social systems where RTS,S research takes place, community engagement and family structures differ from the West - where individual autonomy reigns. This communitarian way of life means that obtaining informed consent entails "spheres of consent" involving village elders, leaders of extended families, or heads of households who are often required to consent prior to the parents of the participants (IJsselmuiden & Faden, 1992; Weijer & Emanuel, 2000). The majority of bioethics takes place in the developed world, creating a cultural bias in the guidelines overlooking this key aspect of collectivistic societies (Gikonyo, Bejon, Marsh, & Molyneux, 2008). However Kenya, South Africa(Langlois, 2008) and Nigeria (Adebamowo, Mafe, Yakubu, Adekeye, & Jiya, 2008; Nigeria Ministry of Health, 2007) have called for researchers to strengthen community participation by outlining it in their research ethics guidelines. Strong community relations and local engagement brings autonomy, transparency and respect to the work of the researchers, but also from a utilitarian perspective, it will strengthen the community's relationship in the long-term with research. Thus, the questions that have remained

largely unexplored with regard to respect for autonomy in clinical trial research through the lens of RTS,S are:

1. Are all options explored to ensure transparency when faced with communication challenges?
2. Who is responsible for ensuring that consent obtained is truly informed?
3. How are parents informed and how do they formally consent?
4. Is community engagement occurring and are local customs respected?
5. Are individual participants being informed through community outreach?
6. Are individuals opting out of the study treated respectfully?

Beneficence and non-maleficence

To adhere to the principles of beneficence and non-maleficence, those involved in the execution of clinical trials must have the welfare of the participants as the goal of the study. The creation of a new malaria vaccine is a benevolent act, however unintentional harm may coincide with its implementation. Malaria epidemiological patterns are difficult to predict in response to intervention, and historical records from research carried out in endemic regions provides evidence for resurgence and, in some cases, shifts from a stable to an unstable disease pattern (Carneiro et al., 2010; J. M. Cohen et al., 2012; Fadare et al., 2010; Graboyes, 2015). In malaria endemic regions, the risk of mortality shifts to morbidity at around age five. However, preliminary evidence from the WHO suggests that severe malaria is starting to occur at later ages in children living in RTS,S research sites (Malaria Vaccine Funders Group, 2013). This places an emphasis on the need for long-term monitoring and evaluation of research sites following the conclusion of a vaccine clinical trial (Snow et al., 1997).

Vaccination campaigns often argue that for the greater good, on the grounds of herd immunity, those eligible for vaccination are obliged to do so – carrying a heavy dose of paternalism. Herd immunity stipulates that if the majority of the population is protected from a

disease (vaccinated) there is a reduction in disease circulation, thereby conferring protection to those unable to be vaccinated (Hendrix, Sturm, Zimet, & Meslin, 2016). As RTS,S only provides modest, waning protection, there is no significant herd immunity. Additionally, the benefit: harm ratio is higher than with most other childhood vaccines which are 90%-99% effective. With RTS,S 64% of children will be exposed to the potential harm of vaccination without a perceived benefit. Additionally the mortality rates are higher amongst girls enrolled in the clinical trials than boys (Klein, Shann, Moss, Benn, & Aaby, 2016; WHO, 2016). As such, the potential harm RTS,S participants are exposed to must be carefully balanced with public health goals - and to better understand these harms, long-term commitments from researchers and funding bodies are required.

In summary, a vaccine which reduces the burden of malarial disease through protecting those most vulnerable to severe disease is providing a benefit to the local population (Alonso, 2006). However, the thorny dynamics of malarial disease call into question the unforeseen long-term consequences of such an endeavor and demand closer epidemiological monitoring. The questions that I thus consider to be most important with regard to beneficence and non-maleficence are:

1. Are participants exposed to an unfair level of risk?
2. Are researchers committed to monitoring the causes of mortality and the accompanying epidemiology?
3. Are historical events informing the modern day RTS,S research studies?
4. Are researchers responding to the WHO's identification of the safety signal linked to gendered mortality?

Justice

The principle of justice in bioethics calls for all individuals to be treated equally, that one society does not have to carry the burdens of another (Kruger, Ndebele, & Horn, 2014). A malaria vaccine will have a major impact on public health in sub-Saharan Africa, yet safe development and equitable access to such a vaccine is hugely impacted by resource availability (J. Cohen, Nussenzweig, Vekemans, & Leach, 2010; Penny et al., 2016). The vaccine is being tested in

endemic regions, reflecting the health needs of the region, an important component of localized medical research. Yet members of rural communities where RTS,S research takes place often have little political power, education, knowledge of medical interventions, resources and have a dire need for medical care – enhancing the vulnerability of the participants to exploitation (Glantz, Annas, Grodin, & Mariner, 1998).

As the malaria vaccine transitions out of clinical trials and into pilot studies the needs of the local communities must be balanced with the wishes of the researchers (Graboyes, 2015). The principle of justice calls on us to work towards reducing the burden of malaria in the developing world through increasing access to interventions and developing new methods to do so; both of which require resources from high-income countries and donor organisations (Jamrozik, Fuente-Núñez, Reis, Ringwald, & Selgelid, 2015). *Inter alia*, it requires us to share the burden of malaria and conduct vigilant research committed to the well-being of local people, preventing further impoverishment of the families and communities. The questions that I thus consider to be most important with regard to justice are:

1. Are participants being recruited in a fair and just way?
2. Are long-term financial commitments in development?
3. What are the responsibilities of the researchers now that the clinical trials have completed?
4. If the participants are carrying the burden of being enrolled in the study, are their communities prioritized as implementation settings? Should the costs be subsidised?
5. Is there a plan in place in the event that studies end because of poor uptake or the loss of a funding body?

Relational ethics

Where the foundation in biomedical ethics rests on the principles outlined above, when it comes to research involving human communities the critical piece of human relationships also comes into play. Specifically, relationships that form during the years that the clinical trial is active in a community. Part of the investigation in this thesis will focus specifically on the relationship

between participants and their caregivers with the research team conducting the trial. Relational ethics is an important aspect to consider during interactions between these actors. Relational ethics runs on the premise that ethical judgements are made in the context of relationship and therefore needs to be recognized as a morally significant player in the decision-making process (Sherwin, 1992). This moves beyond the principles outlined above, where the participant and researcher are viewed as strangers. Instead, one recognizes that researchers may experience moral distress when trying to balance their obligations to sponsors or research institutions with their moral duty to the caregiver and participant.

Where principal-based ethics, or formal ethics, provides a foundation on which we can review research protocols, relational ethics allows for a more expansive interpretation that is situated in the context of the trial stakeholders. Relational ethics can therefore play two roles. One, it can help us understand the principles and their applications, for instance how autonomy can be interpreted based on the relational context in which they are applied. And second, relational ethics can mean being in relation with someone and the generation of duties to that person which correspond with the relationship. This falls outside of the ethics of principalism and creates a genuine source of further duties or obligations.

Some of the aspects I will investigate through the case study are the decision-making and consent processes, the embodied reality of the researcher and the presence of power dynamics. The notion of relational ethics runs through relevant principles such as *solidarity*, *benefit-sharing, embodied accountability* and *relational duty*. *Solidarity* can be used as a way to recognize that any human actor and their identity is shaped by their social interactions. I look at *benefit-sharing* as a call for the actors involved to reflect mutual-respect in the benefits accrued by each group. The role of *embodied accountability* outlines actor decision-making as multi-dimensional, depending on cognitive, affective and emotional experiences. Finally, *relational duty* serves as a way to acknowledge power differentials, based on the norms of equity and complementary reciprocity, having responsibility to one another and recognizing power discrepancies without the exclusion of the other (Pollard, 2015).

THE BROADER PICTURE

The case study and clinical trials in low-resource settings

Above I have outlined the details of the case study, why the PMVT serves as a useful case study to investigate clinical trial conduct in low-resource settings, and the foundational ethical principles and their relevance to the PMVT. I have chosen to focus on the bioethical principles as a starting block as we base our institutional reviews of clinical trial protocol on these. With these fundamental principles as a foundation, I will build my investigation into the ethical challenges associated with clinical trials in low-resource settings.

Research objectives

The research objective is to identify the ethical challenges and corresponding implications for future clinical trials in low-resource settings using the RTS,S malaria vaccine as a case study. Taking the considerations above, the original research conducted during this PhD project aimed to capture the perspective of both the caregivers of pediatric participants in the clinical trial and the research team in the PMVT. The four papers that follow move through these topics in the following ways.

The first paper, *RTS,S malaria vaccine pilot studies: addressing the human realities in large-scale clinical trials,* is a commentary on the RTS,S clinical trial and outlines the clinical trial experiences in relation to the upcoming pilot implementation. It explores the relationship between researchers, participants and the communities where the research takes place. Based on this exploration, recommendations are made with regards to the pilot study implementation and clinical trial design for low-resource settings.

Following this introduction into the PMVT, the second paper, *Clinical trials in low-resource settings: the perspectives of caregivers of paediatric participants from Uganda, Tanzania and Kenya,* is a result of empirical research aimed at understanding the caregiver experience in a PMVT. The data collection involved 78 in-depth interviews with parents of children enrolled in the RTS,S malaria vaccine phase III study or, as a control, the GMZ2 malaria vaccine phase IIb study. Through speaking to caregivers and inquiring about their experience consenting on behalf of the pediatric participant as well as the overall research experience, a deeper assessment of the ethical challenges experienced by this group of actors (caregivers) can be made.

I begin by presenting this empirical data reflective of the caregiver experience and follow it with the third paper, which investigates the researcher experience. As the caregivers introduce the challenges associated with clinical trials in low-resource settings, the researchers provide their perspective and experience. I frame the researcher experience using complexity theory, highlighting that when clinical trials enter the community, they form one complex adaptive system (CAS) together. This third paper is the result of twelve qualitative in-depth interviews with members of the RTS,S malaria vaccine phase III clinical trial in Kenya. Here I identify the main challenges researchers experience when working in the community and the ways in which they deal with this.

In the fourth paper I bring together the experience of the researcher and the caregiver explored in the earlier papers and formulate simple rules that govern the clinical trial system. These are based on the interviews with both caregivers and members of the research team and serves to frame the ethical challenges around a CAS model.

The final theoretical discussion looks to explore the ethical challenges in further detail as well as recommend ways in which to respond, the implications for research and the duties associated with the different actors in the clinical trial system.

RTS,S MALARIA VACCINE PILOT STUDIES: ADDRESSING THE HUMAN REALITIES IN LARGE-SCALE CLINICAL TRIALS

Journal: BMC Trials
Publication date: May 2019

Machteld van den Berg [a,b,c], Bernhards Ogutu[d, e], Nelson K. Sewankambo [f], Nikola Biller-Andorno [a], Marcel Tanner.[b,c]

a. Institute of Biomedical Ethics and History of Medicine, University of Zurich Winterthurerstrasse 30, 8006 Zurich, Switzerland

b. Swiss Tropical and Public Health Institute, Socinstrasse 57, 4051 Basel, Switzerland

c. University of Basel, Petersplatz 1, 4001 Basel, Switzerland

d. Kenya Medical Research Institute (KEMRI), Mbagathi Road, Nairobi, Kenya

e.CREATES, Strathmore University (SU), Madaraka Estate, Ole Sangale Road, Nairobi, Kenya.

f. College of Health Sciences, Makerere University, Upper Mulago Hill Road, Kampala, Uganda

Key words: malaria vaccine, pilot studies, low-resource settings, community engagement, ethics, transnational clinical trials

ABSTRACT

A malaria vaccine as part of the integrated malaria control and elimination efforts will have a major impact on public health in sub-Sahara Africa. The first malaria vaccine, RTS,S, now enters pilot implementation in three African countries. These pilot implementation studies are being initiated in Kenya, Malawi and Ghana to inform the broader roll-out recommendation. Based on the malaria vaccine clinical trial experiences, key ethical practices for effective clinical trial research in low-resource settings are described. For successful vaccine integration into malaria intervention programs, the relational dynamics between researchers and trial communities must be made explicit. Incorporating community values and returning to research practices that serve the intended benefactors are key strategies that address the human realities in large-scale clinical trials and pilot implementation, leading to positive public health outcomes.

INTRODUCTION

In 2017 malaria was attributed to 435 000 deaths and nearly half the world's population was identified to be at risk of infection. Malarial disease carries an immense public health burden, and those at the highest risk for malaria are children living in endemic regions; it is estimated that 266 000 children under five years of age died from infection in 2017 (WHO, 2018b). Since the year 2000 significant work has been done towards reducing the burden of malaria, with much progress made (Bhatt et al., 2015). This success is largely owed to insecticide treated bed nets (INTs), indoor residual spraying (IRS) and artemisinin-based combination therapy (ACTs) also contributing to a 40% reduction in clinical disease and a 50% reduction in *Plasmodium falciparum* infection (Bhatt et al., 2015). While these figures looked promising, they were still far short of the WHO target of 75% reduction in malaria burden by the year 2015 (Roll Back Malaria Partnership/World Health Organization, 2008). In order to achieve this reduction, more tools are needed – including effective vaccines, especially in high-transmission areas.

There are currently a number of vaccines in the pipeline for malaria, in both pre-clinical and clinical development, targeting both children and pregnant women (WHO, 2017c)(4). These target varying stages of the malaria parasite's life-cycle and are categorised as pre-erythrocytic vaccines (PEV), blood-stage vaccines (BSV), transmission-blocking vaccines (MSTBV) and combination vaccines. Despite a robust pipeline, long-lasting sterile immunity against malaria with these vaccines is unlikely and a vaccine will instead serve as a tool to be utilized in combination with other intervention methods. Due to the high burden of disease, a vaccine with a modest level of protection would translate into a significant impact given almost half a million annual deaths. Today there is cautious optimism for a modestly effective vaccine called RTS,S

developed in partnership by PATH Malaria Vaccine Initiate (MVI), GlaxoSmithKline (GSK) and a number of academic and research institutions.

RST,S is a pre-erythrocytic vaccine that has been in development since 1987 and concluded phase III testing in early 2014. The phase III studies adhered stringently to all aspects of formal research requirements, such as Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) guidelines; every effort was made to standardize the process. This large multi-national trial enrolled 15 459 infants and was carried out at 11 clinical trials centres in 7 countries (Burkina Faso, Gabon, Malawi, Mozambique, Ghana, Tanzania, Kenya). RTS,S has been shown to be most effective in children aged 5-17 months, who receive three doses of the vaccine and then a booster at 20 months of age, reducing the cases of severe malaria by 36% (RTS,S Clinical Trials Partnership, 2015a).

The next step for this vaccine is pilot study roll-out in Kenya, Ghana and Malawi. In these three selected countries the Ministries of Health will work together with the WHO to establish the Malaria Vaccine Implementation Program (MVIP). In addition to the efficacy and safety profile, these pilot implementation studies will shed light on the programmatic feasibility of RTS,S in real-life settings, a factor modelling studies have identified to be a critical component of reaching a significant public health impact (Galactionova et al., 2017; Penny et al., 2016). To adequately assess the feasibility of RTS,S in real-life settings, researchers must engage local communities and carefully consider the ethics and processes of undertaking MVIP in different sociocultural settings. This means acknowledging relational ethics in vaccine studies, community dynamics and vaccine uptake, and a commitment to long-term monitoring of the malaria vaccine program.

THE ROLE OF RELATIONSHIP IN RESEARCH STUDIES

Previous RTS,S studies have placed a lot of emphasis on adhering to regulatory requirements and formal research ethics. What we can learn from other vaccine trials is that the emphasis of formal research ethics is as important as close engagement of the clinical trial team with the community (P. Wenzel Geissler, Kelly, Imoukhuede, & Pool, 2008). Taking the time to build intimate relationships fostering shared ownership of the research synergistically and effectively complements the scientific protocols and formal ethical procedures. Relational ethics and shared ownership play a significant role in determining the effectiveness of malaria vaccine studies. Much of the success of a malaria vaccine trial in The Gambia has been attributed to intimate kinship-like relationships between the trial community and field workers (P. Wenzel Geissler et al., 2008). This kind of a relational interaction fosters close collaboration between researchers and communities to confront social and political circumstances. Through this interaction it was found that even in contexts where parental awareness of the RTS,S vaccine was low, there remained a keen desire to enrol children in RTS,S vaccination programs if made available. Based on this work, recommendations have been made around disseminating information specifically to mothers about the vaccine that considers the social and political realities that participants inhabit (Romore et al., 2015). In Tanzania, stakeholders have expressed a positive opinion of the vaccine but have drawn attention to the need for an inclusive communication strategy that incorporates communities and local health care professionals in a culturally appropriate way for that positive opinion to endure (Mtenga et al., 2016). These examples shed light on the need to critically assess processes and ethical conduct during large-scale clinical trials to ensure effective incorporation of the tool into integrated malaria control and elimination programs; considerations that stretch beyond a confident safety profile.

The international community has set ambitious goals for malaria by 2030 and has put RTS,S on the table as a tool to be used in an integrated approach with other malaria interventions (World Health Organization et al., 2015). As we move forward these relational aspects are of particular importance to foster a concerted effort across scientific disciplines and stakeholders from varying sociocultural backgrounds. By harnessing lessons learned from previous malaria vaccine clinical trial experiences, effective integration of this vaccine into malaria control programs is possible in richly diverse sociocultural contexts.

COMMUNITIES AND VACCINE UPTAKE

Strong community relations and local engagement has the potential to bring autonomy, transparency and respect to the work of the researchers. From a utilitarian perspective, it can strengthen the RTS,S malaria pilot study in the selected sites. The RTS,S phase III studies had Community Advisory Boards (CABS) which consisted of influential community members who supported the communication between communities and researchers. These have been effective and therefore need to be further strengthened to involve additional stakeholders with interests in the community and the children's welfare at large (Shubis, Juma, Sharifu, Burgess, & Abdulla, 2009). Acknowledging fundamental intelligence within communities and translating this into the execution of these pilot implementation studies will propel us toward the goal of RTS,S informed choice and acceptance within the community setting. Listening to the voices of the community and integrating these into the study design leads to greater research vaccine uptake (Duan, 2005; Lavery, 2018; Pratt & de Vries, 2018). Failure to do so heightens the power disparity and reduces optimal integration.

LONG-TERM MONITORING OF STUDY SITES

In malaria endemic regions, the risk of mortality shifts to morbidity at around age five. However, modeling studies suggest that severe malaria is likely to occur at later ages in children living in RTS,S research sites (Penny et al., 2016). This places an emphasis on the need for long-term monitoring and evaluation of research sites. This sustained long-term monitoring is often resource consuming but is critical in understanding the impact of interventions and shifting disease epidemiology. Through the collection of narratives and genuinely engaging with community members to share their experiences, potential risks can be followed-up, flagged and clinically investigated. Ethical conduct does not only conclude at obtaining informed consent, it continues into research, monitoring and implementation. The transition in age for severe malaria needs to be explained to the communities – that it is not related to the vaccine deployment but rather a change in the disease prevalence. This, if not explained well, may affect the uptake of the vaccine over time.

Some may challenge the feasibility of relational engagement that is context-sensitive to the MVIP sites, however substantive evidence indicates that close community engagement is a favourable approach to the research in question and does not introduce biases and dependencies of concern at the ethical or research outcome levels (ENDA Graf Sahel, 1993; Jagosh et al., 2012; Lantz, Israel, Schulz, & Reyes, 2017; Rhodes, Malow, & Jolly, 2010). We therefore argue that this can be streamlined and, on the contrary, strengthen the efficiency of the pilot studies. Communities can always provide key insights and facilitate researcher familiarization with the research setting. This, in turn, allows for effective planning and site organization, two factors that have been identified to be key contributors to streamlining the efficiency of clinical trials (Vischer, Pfeiffer, Limacher, & Burri, 2017). Through encouraging dialogue during initial

introductions and building relationships that encourage communities to speak up, to feel safe when doing so, and report when adverse events occur – time will be saved and researchers can ensure a more benevolent process as the monitoring is intrinsic to the study. Previous studies looking at the benefits of community engagement support these claims, suggesting enhanced ownership of the research by local communities strengthens the effectiveness of the research (Gikonyo et al., 2008, 2013; Nyika et al., 2010; Wendler & Shah, 2015). Combating the thorny dynamics of malarial disease without this approach can lead to the aggravation of adverse events and mistrust in the community of vaccination research as a whole (Gikonyo et al., 2008; Nyika et al., 2010). Therefore, it is the responsibility of those who will conduct the pilot implementation studies to call upon the communities to work alongside them for support when incorporating the distinctive values, social and cultural practices to build trust and ultimately strengthen the social value of RTS,S.

CONCLUSIONS

Reaching coverage across the target population and creating an integrated, tailored approach alongside other malaria interventions will determine the extent of the public health impact a malaria vaccine will have (J. Cohen et al., 2010; Penny et al., 2016). This means a keen awareness of local prevention and treatment practices as well as transmission patterns. Vaccines in the development pipeline targeting parasitic diseases cannot be compared to the well-known highly efficacious vaccines of the childhood diseases caused by bacteria and viruses. Parasites have very complex, virtuous life cycles with sexual and asexual development cycles in different niches of the hosts and thus current efforts lead to only partially efficacious vaccines, that still show a significant alleviation of the disease burden (Delany, Rappuoli, & De Gregorio, 2014).

Consequently, working with partially effective vaccines, and tools in general, heightens the emphasis we must place on rooting research in the local social realities to best understand compliance and adherence. RTS,S has an excellent opportunity to set the global stage for shared research ownership, effective community engagement and the development of an integrated, tailored approach to reduce the disease burden.

Declarations

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable

Availability of data and material Not applicable

Competing interests The authors declare that they have no competing interests.

Funding This work was funded by the Swiss National Science Foundation (P0ZHP1_172115), the Canadian International Development Research Centre (IDRC) and the Rudolf Geigy Foundation.

Authors' contributions MV and MT developed the idea for the manuscript. MV wrote the first draft of the manuscript. MT, NS, BO, NBA revised and provided substantial contributions to the arguments and conclusions of the commentary. All authors read and approved the final manuscript.

Acknowledgements Not applicable

CLINICAL TRIALS IN LOW-RESOURCE SETTINGS: THE PERSPECTIVES OF CAREGIVERS OF PAEDIATRIC PARTICIPANTS FROM UGANDA, TANZANIA AND KENYA

Journal: Tropical Medicine & International Health

Publication date: June 2019

Machteld van den Berg [a,b,c], Bernhards Ogutu[d, e], Nelson K. Sewankambo [f], Sonja Merten[b,c], Nikola Biller-Andorno [a], Marcel Tanner.[b,c]

a. Institute of Biomedical Ethics and History of Medicine, University of Zurich Winterthurerstrasse 30, 8006 Zurich, Switzerland

b. Swiss Tropical and Public Health Institute, Socinstrasse 57, 4051 Basel, Switzerland

c. University of Basel, Petersplatz 1, 4001 Basel, Switzerland

d. Kenya Medical Research Institute (KEMRI), Mbagathi Road, Nairobi, Kenya

e.CREATES, Strathmore University (SU), Madaraka Estate, Ole Sangale Road, Nairobi, Kenya.

f. College of Health Sciences, Makerere University, Upper Mulago Hill Road, Kampala, Uganda

ABSTRACT

Objectives: Clinical trials in low-resource settings have unique challenges due to structural and financial inequities. To address this, understanding the setting and factors which influence the decisional process is necessary. This study investigates the experience of caregivers in a malaria vaccine clinical trial.

Methods: We interviewed a total of 78 caregivers of pediatric participants previously enrolled in a phase II or III malaria vaccine clinical trial in Uganda, Tanzania and Kenya. Interviews were analysed using a framework analysis.

Results: Caregivers of participants in this study made the decision to enroll their child based on economic, social and political realities which extended beyond the trial context and into the community and domestic context. The provision of health care was a dominant motivator for participation. Respondents reported social networks, rumours, hierarchal structures, financial constraints and family dynamics affected their experience with research.

Conclusions: Caregiver choice was limited due to structural constraints. The decision to participate in research was embedded in community and domestic hierarchies. Future research should assess other contexts to determine how choice is affected in other low-resource settings when free medical care is offered.

Conflict of Interest statement

The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Uganda: Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee (SBS-441), Uganda National Council for Science and Technology (SS 4297)
Kenya: Strathmore University Institutional Review Board (SU-IRB 0160/18),
Tanzania: Ifakara Health Institute Institutional Review Board (004 – 2017), National Institute for Medical Research (NIMR/HQ/R.8a/Vol. IX/2484)
Switzerland: Ethics exemption (EKNZ Req_2017-00053)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent was obtained from all individual participants included in the study.

INTRODUCTION

Vaccines play a major role in public health and their development is dependent on clinical trial testing in human populations. Transnational clinical trials operate through collaborative partnerships that involve a wide array of stakeholders and participants from varying sociocultural backgrounds. Each of these stakeholders enter into clinical trial research with varying degrees of inequity linked to their role in the clinical trial and resource context (S. R Benatar, 2002; Emanuel et al., 2004). This inequity is of particular relevance for vaccine research operating in low-resource settings due to the discrepancy in resources between the trial centre and the research site in which it operates, which has implications for the choice to participate in research (Glickman et al., 2009).

Phase II and phase III vaccine clinical trials establish the safety of a vaccine and determine its efficacy (WHO, 2017a). These trials involve large groups of participants who are living in the region where the disease targeted by the vaccine is endemic. Due to the operation of phase II and III trials in human communities, the social structures in the clinical trial site are highly relevant to the clinical trial design. To maximise the effectiveness of vaccines currently in clinical trial development, research needs to be sensitive to the social systems within the context in which they are operating (S. R Benatar, 2002; Emanuel et al., 2004). To gain a substantive understanding of the social system in the clinical trial site, communities must be engaged and voices of participants and their families heard (Glickman et al., 2009; Lavery, 2018; Loff, Jenkins, Ditmore, Overs, & Barbero, 2005; London, 2005; Pratt & de Vries, 2018). This engagement process provides insight into the decision-making structures around trial participation, communication needs and the interests of the community in the trial context.

This study investigates the community context, communication needs, and decision-making processes of the caregivers of participants in a phase II and phase III paediatric malaria vaccine clinical trial (PMVT). Each of these trials operated in low-resource settings in multiple African countries. The phase II vaccine trial involved GMZ2 malaria vaccine and was conducted at five clinical trial centres in four African countries (Sirima et al., 2016). The phase III trial involved RTS,S malaria vaccine and was conducted at 11 clinical trial centres in seven countries (RTS,S Clinical Trials Partnership, 2015a). Operating across social systems, these transnational clinical

trials provide insight into the impact that vaccine clinical trials have on the local population while adhering to standardized clinical trial protocols. Local systems and cultures influence decision-making in clinical trial research and mapping the country-specific context supports successful transnational research for development (Hahn & Inhorn, 1999; Helman, 2007; Ward et al., 2017). This study takes these clinical trials as case studies to map the country-specific context and shed light on the caregiver and community experiences in clinical research in low-resource settings.

The phase III RTS,S clinical trial investigated here has led to the regulatory registration and the roll-out of the RTS,S vaccine in a phase IV study, making it the first licenced malaria vaccine. These phase IV studies will take place in three different countries, including the Kenyan research centres investigated here (WHO, 2018a). This makes the experiential understanding of the research participants, their caregivers, and communities in the context of the clinical trial centre even more pertinent.

While community engagement has been recognized as necessary in ethical transnational research, there is no clear consensus as to its definitive application in different community contexts (Tindana et al., 2007). Context may influence the ways in which benefits and risks are perceived by the participants, particularly in settings with large resource inequities (Cottingham & Fisher, 2016; Walker, Cottingham, & Fisher, 2018). Using knowledge of the health and social structures to inform community engagement practice is a critical component of designing research studies appropriately (Miller et al., 2010). Researchers conducting clinical trial studies in low-resource settings can integrate the findings of this study to protect participant autonomy through integrating them into the communication of trial procedures.

METHODS

In order to better understand the experiences and decision-making processes of caregivers during PMVT we conducted a series of in-depth interviews between March 2017 and March 2018 with caregivers of children who participated in a PMVT.

Sample population

Interviews were held across four different clinical trial sites in Uganda (Iganga), Kenya (Siaya and Kombewa) and Tanzania (Bagamoyo) with caregivers of participants. We used purposive sampling to recruit respondents and in the majority of the cases the mother was the primary caregiver. The interviews were semi-structured and held in the home of the respondent.

Trial

RTS,S phase III malaria vaccine trial was carried out between March 2009 and January 2014 in 7 African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, United Republic of Tanzania) and spanned across 11 clinical trial centres (RTS,S Clinical Trials Partnership, 2015b).
GMZ2 phase IIb malaria vaccine trial was carried out in April 2010 - July 2012 in 4 African countries (Burkina Faso (2), Ghana (1), Uganda (1), Gabon (1)) and spanned across 5 clinical trial centres (Sirima et al., 2016).

Study design

This was a qualitative study that utilized in-depth interviews to capture the perspective of the caregiver who had a child enrolled in a PMVT. The field work consisted of a scoping trip to the research sites to introduce the study, recruit participants and meet with community leaders. The field visits took place in March 2017 (the scoping visit) and the interviews were conducted between May 2017 and March 2018 with the help of local research assistants. The research

assistants from Tanzania were fluent in Swahili (one female and one male). From Uganda all three female research assistants were fluent in Luganda and conversational in the related Lusoga language of the community investigated. In Kenya all three research assistants (1 male and 2 female) were fluent in Dholuo. None of the research assistants lived in the community investigated, all were fluent in English and had post-secondary education. Interviews were semi-structured and had a focused discussion on the vaccine trial, leaving room to explore concepts as they emerged, such as community dimensions and domestic relationships in the context of the trial. Funneling was applied, where interviews began by asking open questions and were then funneled into more specific questions about the respondent's views and experiences within the health system, interaction with researchers, and challenges faced in the community. The interviews were recorded with the informed consent of the respondent and conducted in the local language. They were then transcribed verbatim and translated into English by the research assistant. The interview guide was first piloted in each country and then changed and developed throughout to best explore unanticipated replies as they emerge.

Ethics

The study protocol, informed consent forms, interview guide were reviewed and approved by the following bodies. In Tanzania: National Health Research Ethics Review Committee for the National Institute for Medical Council (NIMR); Ifakara Health Institute IRB (IHI-IRB); Tanzania Commission for Science and Technology (COSTECH). Uganda: Uganda Council for Science and Technology (UNCST); the Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee (SBS-HDREC). Kenya: Strathmore University IRB (SU-IRB).

Analysis

The analysis was based on the approach described by Strauss and Corbin (1998) (Strauss & Corbin, 1998). First a detailed line-by-line microanalysis was conducted to identify categories in the data, this was followed by an exploration of the categories, their properties and the relationships between them. This was then discussed between the first author of this paper and

the local bilingual research team to ensure the accuracy of the analytical process. These categories were defined into main themes as illustrated in figure 1. These themes were then integrated into a framework to define the scope of the analysis and are presented in the results.

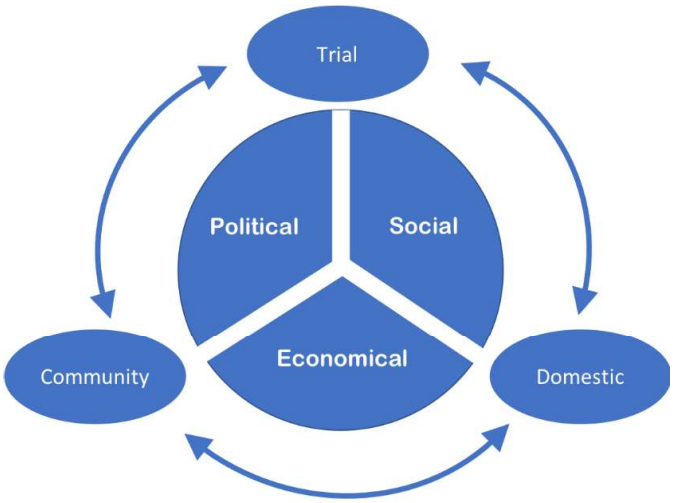

Figure 1. Framework for analysis outlining the interplay between community, domestic and trial contexts that the respondent inhabits and the economic, political and social realities of the embodied respondent.

RESULTS

Of the 78 interviews a total of 23 were with parents of children enrolled in the GMZ2 Phase IIb trial in Iganga, Uganda. The remaining 55 in-depth interviews were with parents of children enrolled in the RTS,S phase III study across three sites in Bagamoyo, Tanzania (n=18), Kombewa, Kenya (n=20) and Siaya, Kenya (n=17). Interviews lasted around 31 minutes on average, with the longest being 56 minutes and the shortest being 19 minutes. Seven interviews could not be included in the time calculation due to logistical limitations of the recordings.

The respondents made it explicit that they inhabit multifaceted realities falling under clinical trial, community and domestic contexts. Each of these themes is shaped and embedded in their economic, social and political reality (Table 1).

Setting	Dominant Themes
Trial context	• *Social networks reported on high-quality care* • *Trial centre vs. government facility medical care* • *Social skills of trial doctors* • *Outlier: trial led to rumours and was then impacted by the rumours.*
Community context	• *Community valued health care* • *Reassured by friends about participation* • *Health benefits should be for the whole community* • *Trial improved conditions in the community* • *Local leadership influences community acceptance* • *Outlier: Rumours impacted social life*
Domestic context	• *Individual context leads to trial enrollment* • *Valued health care and improved condition of child* • *Fathers influenced enrollment, consent and withdrawal.* • *Explicit reality of sick child in the home* • *Outliers: Trial interfered with domestic harmony*

Table 1 Respondents reported their experience of the trial, community and domestic context. The dominant themes that arose during the interviews are displayed.

Trial Context

Respondents frequently began by explaining their trial experiences and defined the role the trial played in their lives. They did not view the clinical trial as detached from their lives, instead participation was motivated by an array of political, social and economic factors unique to their lives.

The mainstream opinion in this sample of respondents was a great appreciation that the trial provided free, high-quality medical care for their child during difficult economic conditions.

> *R40: Before the research study, when you visit the government hospital after tests they were telling you to go buy medicines and sometimes you don't have the money. But after my child joined the study the situation changed. I am grateful my child was getting malaria tests and given medicines in a sealed bottle not the opened ones.*

The contrast between the free medical care in the study and the options available to the parents through government hospitals was consistently highlighted by respondents.

> *R56: We were comfortable because the health workers were approaching us well, they had good manners. At times you may go to the hospital and they tell you that you are stupid, but these ones were good health workers, they could tell you to do something and you accept because of their approach.*

The trial was also not independent from circulating rumors within social networks. Where the mainstream in this sample reported an appreciation for the trial and the medical benefits, a few outliers noted the impact rumors had on the way the study was perceived and pushed back against them.

> *R34: Someone can spread rumors. We would tell them to go and see for themselves that there is nothing negative taking place. My child who is in the study is healthier than yours who is not but you keep talking about blood draws. You destroy the image of the study for nothing.*

Community Context

The community played an integral role in the uptake, acceptability and integration of the clinical trial into the local setting. Caregiver decision making was intimately tied to their relationship with others in their local community.

> *R46: Before joining I used to see my friends going and I guessed it would be a good project. When I joined, I was assured, yes, it was a good project based on their procedures and services given.*

A number of participants reported that the benefits of the trial should be available to everyone. Placing an emphasis on the need for the high standard of health care to be extended towards other members in the community.

> *R32: Your neighbor ought to enjoy what you enjoy. The fruits you enjoy, he ought to enjoy.*

Respondents often reported from the perspective of the community and how the trial improved conditions for the children of their community as a whole, despite a lack of financial resources.

> *R35: The people were enrolled praised the study. Most of them are the people who come from around who earn a little money. Sometimes when the child falls sick it becomes difficult especially for us who are farmers. They would give the children effective drugs. So, the people around consider it good.*

The local political leader has a significant influence on the trial. When the local leader is trusted by the community members and this individual approves of the trial, then the study participants will be much more comfortable.

> *R64: Our chairman as you have seen him, he is good. Whenever the study people would leave, he could explain to us what was going on, so that's how you could pick to participate. These ones who came straight to the chairman we knew that they are people of light, because we knew that someone who has not*

come through the chairman is the one you can doubt but someone who has come through the chairman, there is no need to question.

Where the mainstream in this sample reported satisfaction with the clinical trial, some outliers also reported cases where community members challenged the clinical trial and those enrolling their children.

R65: Because at first the people were asking, why do you need our children? Which kind of check-up are you doing? What are you checking? As you know the village life we are in.

Domestic Context

The caregivers of participants in the PMVT repeatedly spoke about the role that the trial played in their lives at home, in particular how the family's access to medication influenced their participation.

R14: My child she was very sick and when I went with her to the hospital I found the government sector had no drugs and the study did have drugs. So I went and found a sister and she asked me if I could agree to join the study, "if you agree to join then I will take you so that your child can be helped and if you refuse, you can go to other district hospital but even there are no drugs" So I sat with her and asked her and she had already told me that the study is very good. I asked her if they can help me and she said yes, only if I agree to join, and I said yes I have agreed to join and for sure they treated my child.

Facing financial challenges within the domestic settings and then having the clinical trial provide free and high-quality care for the sick children was positive according to caregivers.

R66: I benefitted because my child is still alive.

R35: My child would be given medication even when I didn't have cash. They would also give me fare back home. It was good. Anytime I would take the child to the hospital, they would treat him.

Fathers played a significant role in participation and many respondents who were mothers elucidated the role the father had in motivation and consent to join, or withdrawal from the study.

R17: Others also took it seriously that those people are removing a lot of blood from the children. So they did not agree, and other people, including the fathers of the children never agreed which is why they didn't join.

Caregivers also explained what it means for them to have a sick child within the home, particularly how it could also lead to problems within the relationships. For the majority of participants this was improved when the children could participate in the study.

R56: You need to eat yet the child is sick. You eat late because food is prepared late, you quarrel and can even fight. Such things happen and there is no love in the family because every time you are concentrating on the child. You may find that even some men get other women, complaining that they are fed up of the other one because her children are sickly.

While the mainstream opinion in this qualitative sample expressed appreciation of the trial and the way in which it benefited the families, in some exceptional cases participation in the trial could lead to problems in the spousal relationship.

R78: They were removing a lot of blood. Maybe they just needed a lot. I was afraid that he will collapse and his father will beat me up. I was afraid but there were some women that we went with who encouraged me to go.

DISCUSSION

The findings of our qualitative in-depth interviews with caregiver of participants enrolled in a PMVT provide insight into the values that caregiver hold, what motivates their participation, and their experience in the clinical trial. The primary motivation for participation drew from each theme (trial context, community context, domestic context) and is intricately connected to the political, social and economic reality that a caregiver occupies at a given time. Below we move through these themes and discuss the role local values and beliefs play in research participation.

What is most striking about our results is the dominance of free medical care as being the prevailing motivator for participation. Limited capacity of local medical services has been raised as a challenge in transnational research when the medical services in the clinical trial significantly surpass local services (Mtove et al., 2018; H. T. Shapiro & Meslin, 2001). It is cross-cutting across all themes analysed in our study and is repeatedly emphasised by caregiver of participants enrolled in the clinical trial as being the most valued and positive component of the research trial. This finding illustrates the interplay between the local structural limitations and trial enrollment, having significant implications for individual decision-making processes concerning the trial (Chuan & Schaefer, 2015; Paré Toe et al., 2013). Having a powerful motivating factor, such as the provision of care in this context, prevalent across all themes is indicative of local structural constraints. The provision of care to participants in clinical trial research is presented as 'benefit-sharing' where the clinical trial aims to give back to participants. This 'benefit-sharing' with individual participants in a setting where the institutional health care structures are limited may impede choice with regards to enrolment (Hayden, 2007). Failing to balance the provision of care with concise communication around trial proceedings to the caregiver can lead to an 'empty choice' where structural factors around health care eliminate an autonomous decision (J. A. Fisher, 2013; Kingori, 2015). A caregiver of a participant will be limited in their autonomy when faced with the decision to enroll when it is their only means to ensure their child's health. This is relevant for both informed consent, but also risk versus benefit communication in transnational clinical trials (J. A. Fisher, 2013; Molyneux, Peshu, & Marsh, 2005; Mtove et al., 2018).

Beyond the individual, the provision of accessible medical care was also highlighted as the trial component most highly valued by the community. Health care was framed as a community value by respondents. The political leadership which influenced community acceptance of the research suggest a locus of decision making that is communal. The leadership in the community decided its position on the research study and then passed this approval down into the community, driven by the desire to promote the health of the children. The provision of health care within the community context in combination with the structural constraints, impact decision-making structures in clinical trials and provide challenges for the consent process (Fitzgerald, Marotte, Verdier, Johnson, & Pape, 2002). Communal decision making extends beyond traditional liberal political philosophical notions of autonomy and informed consent, this contextual reality was described by one caregiver as "*the village life we are in*". The respondents are embedded in communal lives where other members of the community would suggest their child was going to be killed or face the consequence of a stigmatized condition if they enrolled in the PMVT. Failing to recognize the contingency of community and individuality and to overlook the historical experiences that contributed to the generation of these beliefs can derail research studies (Kingori, Muchimba, Sikateyo, Amadi, & Kelly, 2010). Our results, in combination with the contingent notion of community in informed consent processes, place an emphasis on the need to clearly communicate risks and benefits to the trial community so that they are not overshadowed by the benefit associated with health care provision.

The final analysis of the domestic context also brought the value of health care provision to the forefront as the dominating motivator for trial participation. Having a sick child in the home leads to difficulties for others sharing that same domestic setting, whereas having access to health care to treat the sick child leads to greater domestic harmony. Respondents reported that enrolling in the research trial often occurred as a result of the difficulty in accessing medical care and trial enrollment has been reported to be lower in areas with better medical services (H. R. Fisher, McKevitt, & Boaz, 2011). This illustrates the power that the provision of medical care has when it is embedded in a low-resource context, distorting a balanced risk and benefit analysis or leading to the negation of the risks all together.

How parents weigh the risks and benefits of participation differed and was related to the structural constraints around health care access for the child (Kingori, 2015). Health care provided by the PMVT was reported to be highly valued by both parents and improved the condition of the child. This trickled down into having effects on the relationship the mother had with the father as well as the overall "*joy*" in the home. Having a sick child in the home can burden the relationship and make parents more likely to participate in research than when their child is healthy (H. R. Fisher et al., 2011). Individuals living in contexts with few medical services will see medical provision as a much larger benefit to their family than those in contexts with a strong local health system, calling for a tailored communication approach appropriate for each setting.

The absence of risk in the interviews conducted was also of note. Sceptical beliefs or concerns were often framed as "*rumours"* by respondents and those believing them were referred to as a distant third party. Respondents repeatedly emphasized the gratitude they experienced from trial enrolment and the accompanying care. Concerns around potential adverse events outlined in the informed consent documents associated with vaccination did not come up as a significant concern during the interviews. While therapeutic misconception was also evident in some interviews, the offer of medical care over-shadowed it in its ability to influence the caregiver's risk perception.

CONCLUSION

Designing vaccine clinical trials in low-resource settings such that the communication of risk and benefits is done in a way that is comprehended by participants and their communities is a challenging task. Ethical design of research requires the communication of trial proceedings not to be overshadowed by the provision of free care in resource-limited settings. To address this in future trials and taking the first step towards more ethical communication means placing the community at the forefront of research design (D. E. Beauchamp, 1985; Callahan, 2003; V. M. Marsh, Kamuya, Parker, & Molyneux, 2011). Putting the community central to the research means to understand the values present in the settings where the research is taking place and how these are situated relative to the individual and their decision-making processes. This can be

achieved through stronger engagement with local stakeholders and health systems, including strengthening the government health system (Ward, Shaw, Anane-Sarpong, et al., 2018). The second step is to design clinical trials in collaborative partnership with local leadership to foster local capacity building and ultimately strengthen local health capacities (Ward, Shaw, Sprumont, et al., 2018). Being responsive to community needs and integrating values that influence participation in research alongside local leadership can provide a more balanced conception of the risks and benefits. The active involvement of both community and local leadership can support the disentanglement of comprehension barriers while still allowing for 'benefit-sharing'. An iterative process executed by the clinical trial team that engages the community and works closely with local leadership will foster research communication and thereby participant choice.

Understanding and addressing the local context will reduce inequalities inherent in transnational clinical trials in low-resource settings (Launiala & Kulmala, 2006). The utilization of this understanding and its translation into research will support the communication of research appropriate for the local setting (Mwenesi, 2005; Williams & Jones, 2004). This involves integrating the social, political and economic components into clinical trial design and paving the way towards more equitable research practices and infrastructure that enables a real choice for study enrollment.

Limitations of this study include the sampling strategy, which recruited caregivers who enrolled their child and therefore would have been more likely to have a reduced risk perception due to the provision of care than caregivers who were approached and refused to enroll their child in the clinical trial. Future work investigating the perception of caregivers in the community who refused to enroll their child could shed further light on this topic. We also did not interview and male caregivers, which is indicative of the traditional caregiving roles where the mother or grandmother has the primary responsibility for the child's health.

Through mapping how contextual realities interplay with the decision-making process of caregivers of pediatric clinical trial participants, this study can strengthen clinical trials in low-resource settings. Our work shows that individual consent in clinical trials is intricately linked with community consent and family dynamics. Based on this, future research needs to

investigate how this interplay varies across contexts and the role free medical care plays in consent in these settings.

APPLYING COMPLEXITY THEORY TO MODEL THE OPERATION OF CLINICAL TRIALS IN HUMAN COMMUNITIES

Journal: BMC Trials

Submission date: March 2019

Machteld van den Berg [a,b,c], Bernhards Ogutu[d, e], Nelson K. Sewankambo [f], Sonja Merten[b,c], Nikola Biller-Andorno [a], Marcel Tanner.[b,c]

a. Institute of Biomedical Ethics and History of Medicine, University of Zurich Winterthurerstrasse 30, 8006 Zurich, Switzerland

b. Swiss Tropical and Public Health Institute, Socinstrasse 57, 4051 Basel, Switzerland

c. University of Basel, Petersplatz 1, 4001 Basel, Switzerland

d. Kenya Medical Research Institute (KEMRI), Mbagathi Road, Nairobi, Kenya

e.CREATES, Strathmore University (SU), Madaraka Estate, Ole Sangale Road, Nairobi, Kenya.

f. College of Health Sciences, Makerere University, Upper Mulago Hill Road, Kampala, Uganda

ABSTRACT

Background: When a vaccine clinical trial enters a human community two independent systems merge into one system with various levels if interdependence. This system exhibits non-linearity and unpredictability, creating challenges for the research team. In this study we explore the researcher experience during clinical trials in human communities, through the lens of complexity theory.

Methods: We conducted in-depth interviews with a total of 11 researchers working on a phase III vaccine clinical trial in Kenya (Registry name: RTS,S ClinicalTrials.gov; Registry number: NCT00866619; Registry date: March 20, 2009). The interviews captured the researcher's experience of working in a complex adaptive system and were analysed using thematic coding.

Results: Both human communities and clinical trials have the attributes characteristic of complex adaptive systems. Challenges researchers encountered working in this merged system include rumours, suspicion related to blood draws, and misconceptions. The researchers highlighted that a foundation of trust and open communication were foundational blocks to embrace the non-linearity of the system.

Conclusions: We have identified the key role that complexity theory plays in improving clinical trial design. The factors identified by our respondents, as seen through the lens of complexity theory, are integral to informing how clinical trial research can be tailored to the local social setting. Understanding the system (community and trial) as one allowed for the identification of patterns that influence the emergence of the system. This calls for clinical trial design to incorporate iterative practices to better equip research teams to adapt to the emerging behaviour of the system.

BACKGROUND

Clinical trials are a critical part of the vaccine development process to establish both the safety and effectiveness of a vaccine. Vaccine clinical trials have extensive regulatory requirements and operational components to adhere to (WHO, 2017a). These clinical trials take place in human communities where elaborate social networks and environmental factors form the community. When research such as vaccine clinical trials enter into a community, a complex array of considerations come into play and affect the outcome of the research. Considerations specifically relevant to the social complexity of the community and the regulatory complexity of the clinical trial.

There are particular considerations specific to clinical trials being conducted in low-resource settings. The majority of vaccines currently in the development pipeline target diseases endemic to populations living in these settings (WHO, 2019). These considerations are unique due to the large resource discrepancy, with a high-capital vaccine clinical trial centre conducting research in a low-capital clinical trial site within which the communities are located. This has significant implications for communication, benefit-sharing and engagement with the community (van den Berg et al., 2019a). To explore these implications, we take the unique approach of utilizing complexity theory to explore the unfolding of a new complex adaptive system (CAS) when a clinical trial conducts research in a community (Gilchrist, 2000; Mathews, White, & Long, 1999; Neely, 2015; Ramalingam, Jones, & Overseas Development Institute (London, 2008).

Here we investigate the experience of two vaccine clinical trial research teams working in communities in Kenya. We have selected a phase III clinical trial of the leading malaria vaccine, RTS,S, to study the interplay of the research team with the community. This multinational, phase III study was carried out across seven countries/systems and cultures with rigorous, standardized regularity requirements in all eleven trial centres (RTS,S Clinical Trials Partnership, 2015b). These regularity demands on research teams occur in vastly different contexts. With a focus on Kenya, we look through the lens of the researchers working in the community during the phase III malaria vaccine clinical trial. In 2019, this vaccine will be rolled out in phase IV studies in three different African countries (WHO, 2018a). This vaccine clinical trial is therefore characteristic of large, multinational clinical trials operating in a low-resource setting. This clinical trial team has proven to effectively work with the community such that the research will continue into a phase IV study.

Through this evaluation we shall better understand the factors at play when a complex clinical trial system enters a complex social system.

Complexity theory is a useful framework for vaccine clinical trials operating in low-resource settings. Communities and clinical trials are CAS (Gilchrist, 2000; Mathews et al., 1999; Neely, 2015; Ramalingam et al., 2008). The conduct of vaccine trials merge two CAS, the clinical trial and the community, into a new system. In essence, CAS describe systems that have components of non-linearity, iteration, unpredictability, interdependence and emergence (Holland, 2014; Maguire, McKelvey, Mirabeau, & Oztas, 2006; Sawyer, 2005). Cilliers (1998) outlines a CAS as a system with a history that impacts the current state and its evolution, a system that has many concurrent interactions which are characterized by feedback loops and is open to the external environment (Cilliers & Spurrett, 1998). Based on these attributes, the merging of a complex trial system and a complex social system requires prospective considerations for researchers working in vaccine development. To better understand these considerations and their consequences, the experience of researchers in this phase III malaria vaccine clinical trial in Kenya is evaluated. This understanding can strengthen clinical trial through prospective integration into clinical trial design.

METHODS

In order to capture the researcher's experience in the community during a vaccine clinical trial in a low-resource setting, we conducted a series of in-depth qualitative interviews in March 2018 with members of the RTS,S phase III clinical trial. This study was part of a larger project looking at clinical trial research in low-resource settings and the methodology presented here relates to other work (van den Berg et al., 2019a).

Study Design

The phase III transnational clinical trial was carried out between March 2009 and January 2014 covering eleven clinical trial sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, United Republic of Tanzania). Upon the completion of the trial, post-trial epidemiological monitoring has continued to be done. All respondents were based in Kenya.

In-depth interviews

Interviewees were asked about their role as a researcher in the clinical trial, particularly their role in community engagement, focusing on relational dynamics and communication in relation to the formation of a CAS with the trial team and the community. Questions were also focused on identifying their personal perception of the community, both positive and negative, and the ways in which they responded to those experiences.

Purposive sampling was used, all respondents were researchers involved in the RTS,S malaria vaccine candidate phase III or post-study epidemiological monitoring (ClinicalTrials.gov Identifier NCT00866619). Trust was established by visiting the centre in March 2017 and introducing the study and its aims, maintaining regular contact and then returning to the clinical trial centre in March 2018 to conduct the interviews. The interviews were conducted by the first author, MV, in English at the clinical trial centre. Interviews were conducted until saturation was reached.

Data analysis

Interviews were recorded, transcribed and then coded using MAXQDA software. Transcription began immediately after data collection and inductive detailed line-by-line microanalysis was utilized to identify categories in the data. Based on these categories, relationships were identified and organized into themes. All interviews were conducted, transcribed and analysed by the first author and parts of the coding were reviewed by the co-author SM. The focus of the analysis was on researcher values, lived experience and views on community engagement to best identify the CAS from the researcher's experience.

Ethics

Ethical approval was obtained from the Strathmore University IRB (SU-IRB) in Kenya and written informed consent was obtained from all respondents for the in-depth interviews. All data was anonymized by removing identifying factors and securely stored on a password protected computer.

RESULTS

The results presented here relate to earlier work looking at the experience of caregivers of pediatric participants in malaria vaccine clinical trials (van den Berg et al., 2019a).

Eleven interviews were conducted with members of the research team. Respondents had various roles in the research team but all were involved with the RTS,S malaria vaccine clinical trial. The average length of an interview was 53 minutes, with the shortest being 28 minutes and the longest 2 hours.

In the interviews, respondents described their experience in the community and overall impressions with great detail. Respondents described communities as dynamic and outlined the experiences they had when working in community systems. In particular, challenges associated with blood draws, rumours and misconceptions arose, as well as the ways in which they dealt with these. Often a foundation of trust and continuous communication were reported to be key for clinical trials to work in a community and through complexity theory this foundation can be used to embrace the non-linearity of the system and effectively work in it. Below we present the alignment with these descriptions and CAS, as well as the indicators that when a clinical trial is initiated in a community they merge, and they exhibit interconnectedness and interdependence and behave as one cohesive system.

Communities are complex adaptive systems

The ways in which respondents defined community was strongly aligned with attributes related to unpredictability, non-linearity and emergence associated with complex adaptive systems. When discussing work in the communities, respondents described a dependency on a complex array of factors. Throughout the interviews, researchers brought up their definitions of community from their perspective, in particular the diversity across various communities and the ways in which this impacted the trial.

> *P11 Working with communities is dynamic. There are pros and cons about working with communities. But it depends on how you conduct yourself in the community and how you engage the community.*

P10 It depends on the social make-up of the area where you are. For example, we had more withdrawals from the central area than from the more rural outlying clinics.

Challenges of working in CAS

The impact of misconceptions around adverse events and risks was reported by all respondents, which could vary depending on the community context. These misconceptions arose out of contextual factors within the community system, as there are multiple factors acting on the community simultaneously to the trial procedures. These also indicate the merging of two independent systems (trial and community) displaying significant interdependence. The challenge in dealing with this was also raised, particularly in sensitive cases when a participant has died from causes not related to the vaccine study. Here the community blames the powerful clinical trial for an event where helplessness is experienced in the community, indicative of a power imbalance and linked to the hierarchy characteristic of CAS. The non-linearity and complexity of working in CAS settings was evident, as well as the experience for the researcher being a part of the community system and then having to return to an unpredictable scenario.

P08: If for example after a participant dies, it becomes another challenge altogether because a participant can die from another cause. But then people sometimes feel that in a way you contributed to that. But you see those who are participating at least they know because they went through the whole treatment procedure and everything so then they understand. But now the whole community, even when you are going to visit these compounds you feel when you are going you are not really sure of what can take place, because you are going, and you don't know if maybe some people will turn wild and attack you or something. But then it never happened, really, actually, it never happened.

The interviews revealed consistently that there are many concerns from the community with regards to blood draws and transfusions, illustrating that communities are not operating in isolation, instead they are imbedded in contextual histories where clinical trials were, at times,

exploitative. This overlapped with religious motives for denying medical intervention such as blood transfusion or oxygen for a sick child enrolled in the clinical trial. Many of the communities have rooted beliefs around blood, arising out of these historical research experiences.

> *P08: The main issue in the community is about blood samples that we take, that one is a major issue. People want to know "what are you doing with the blood?"*

There are multiple factors that play into the consent process and it is rarely the person who consents (frequently the mother) who has the only say in the child's participation. The concerns around blood or other misconceptions are often heightened in those family or community members who haven't gone through the formal consent process. Different communities have varying employment realities, which contributes to the social make-up and transience of fathers at a given moment in time. This is not predictable and adds a layer of complexity to operating in a community.

> *P02: Some homes you had the father, or the head of the household, who does not want anything to do with vaccine research because of the perspectives. So they would be hostile. And threatened, "leave my home, I don't want my children in those studies, you're taking blood for what? You're making money with our blood!"*

In a few cases it was highlighted that external research projects being conducted in the area interfered with the perception of the research study. In particular, it was noted how some researchers bypassed community engagement processes. As the community did not necessary distinguish between research institutions due to the overlap of activities, this generated further broad suspicion around medical research.

> *P11: University students that don't know how to do it and they're in a hurry to get their data. They just say, take these 200 shillings, I want to remove the blood of the child. And the community kept on thinking it was us.*

It was widely reported that having local staff was necessary for effective community engagement and necessary for an understanding by the trial team of the sociocultural norms and economic contexts unique to the participants. However, it was also acknowledged that in the event of an

employment termination there could be a disruptive impact on the community-trial relationship. These explicit demands by the community for more reciprocity from the clinical trial was indicative of the community's experience with the power imbalance. The economic and power inequity was seen as a particularly delicate issue for the research team, in line with the hierarchal nature of CAS.

> *P02: There are instances where the family would say "My daughter was looking for a job but you never hire people here from this community, you want to bring people from outside to come and work for you" so probably a percentage of your field team should come from the community, because now the community relates, they know these people, these people live amongst them, there is no way they can bring something bad to them.*

> *P02: We have a family around the community, one of their children was hired here but because of negligence, he used to miss, he lost his job. So the family was mad at the organization so they would go around the community and discourage people from engaging with us.*

How researchers work in complex adaptive systems

It was cross-cutting across respondents how important it was to understand the people in the community, show concern and express gratitude for their participation. This was an important aspect to working harmoniously in the community through strengthening the communication and comprehension. At times, the researchers identified the power imbalance within the CAS between the clinical trial and the community, feeling that more needed to be done for the community and the participants.

> *P02: Think about their needs and don't treat them as a subject, treat them as someone who has sacrificed their time who has put aside some of the things they were supposed to do to come to the clinic.*

P07: You get to learn their challenges, or their fears, or their reservations. And then you get to explain why you are doing what you are doing at that time point and why you are planning to do it or why you are not planning to do it.

Understanding the role of community leaders, especially elected leaders, attributed to positive opinion of the trial within the community – as they can have a major impact in the community and determine the directionality of the engagement. It requires careful engagement by the research team, as it is necessary for the success of the trial to have the chief's support.

P05: And the chiefs, those ones you must have on your side, before you try anything. Because if they decide you treated them disrespectfully that study is not going onwards, they'll say don't enroll, they're doing this, maybe they're selling blood.

Being aware of the norms and subsequently approaching misperceptions in accordance with those norms was reported as being a continual iterative learning process. For instance, addressing power dimensions and sending the appropriate staff member to provide clarification in challenging situations. A few respondents clearly identified how important it is to have members of research team that are culturally versed and sensitive to local norms. Without this there can be implications on perception of the study, without the researcher themselves being aware of it.

P05: He is familiar what not to do. Maybe when you enter a household, how you should enter, who you must see before you start seeing. You can't just enter a homestead and just start talking to anyone you want, it's inappropriate.

Frequently it was reported that staff should not only be properly trained, but also selected based on their fit within the community norms. This was seen as key to maintaining a trusting and strong relationship with community members.

P11: You must know who your staff are. Others are outgoing, others are introverts. You can't send an introvert to the village, they will be closed. The villagers will not share with them.

Respondents often brought up the role that trust plays in communicating with the community and maintaining harmony. The ways in which this was built was through consistent and transparent communication, as well as adhering to the proposed study protocol without surprising the community with new procedures.

> *P09: Trust is in the core of the understanding between the staff and the community.*

Hosting information sessions that are inclusive to all members of the community (not only those who consent and the participants) was reported to be a positive contribution to the trial perception and addressing information gaps. It is helpful to have regular sessions where all can attend and have access to information updates to avoid a powerful voice having a misconception or information gap.

> *P11: Communicate and talk to them at every level. Right from the time they come to the clinic. To not be tired of communicating, communicate all the time.*

Informing the community about research findings was also highlighted by the respondents. Especially in the long-term view of the research study and supporting future recruitment was identified to be tied closely to ongoing engagement and keeping the community informed.

> *P01: I think people want to know where you have reached, because especially if it is not a perfect vaccine, for the lack of another word, then people will need to come back again, provided that the disease remains a problem, to come back again to the community. That's a major challenge, especially for large studies.*

The introduction of a new research project, in this case a new vaccine, required a lot of clarification and engagement. Especially ongoing involvement of the community to raise understanding and comfort with the new tool. The nature of this involvement was dependent on the community the research team was working in.

> *P08: What I have learned in this community, is that if there is a vaccine that is injected, a lot of mobilization needs to be done. Because you find that in these*

areas there are not many vaccine trials that previously had been done so people don't really know how the vaccine trial is done, especially one that is injected.

The establishment of the Community Advisory Board (CAB) was reported to be beneficial as a tool for staying aware of the community developments. Having regular meetings allowed the clinical trial team to address misconceptions and information gaps, as well as adapt appropriately to new situations.

P01: I would not start a study without telling the CAB, it would almost be suicide. If something goes wrong, even if you don't know who to tell, you see then you have already told them "oh remember the study, we discussed, oh this is what is happening" or they already know about it, so if they hear a rumour they can tell the people, we heard, but that is not really it.

A number of respondents identified the need to translate informed consent forms into contextually-sensitive language. It was reported that certain words translate poorly into the local language, with the consequence of creating community suspicion towards the researchers.

P04: Allowing the use of more latitude with how we translate, meaning it should not be word-for-word, which is what they tend to look at, but it should be more context.

Despite the various ways in which challenges were addressed and the overall benefits attributed to the clinical trial working in the community, a few respondents called for more to be done. These researchers felt that with the power of the clinical trial and the benefits received, the community needed to benefit more and the trial needed to do more in return and acknowledge this power discrepancy.

P02: Being an organization working in a community, you should give back to that community. You should show concern, don't just collect data and forget about them.

P07: Different communities have different expectations, it is really challenging because when we are starting the trial the new satellite facilities were looking forward to us doing much facility improvement.

DISCUSSION

Clinical trials carried out in and merging with communities exhibit many attributes of complex adaptive systems including historical influence, dynamic interactions, nonlinearity and interdependency (Cilliers & Spurrett, 1998; Helbing, 2013). A useful definition by Neely (2015) describes a complex adaptive system as *a system in which agents are interconnected and interdependent and their individual actions form patterns of repetition that create emergent structures which have a non-linear influence on agent behaviour and further emergence* (Neely, 2015). Drawing on this definition, the initial state includes an independent community system and an independent trial system, each governed by an independent set of rules. Upon the initiation of the clinical trial in the research site, these systems merge and their components exhibit interconnectedness and interdependence. This leads to the generation of an entirely new CAS with a non-linear influence on system behaviour and emergence, open to the external environment. Through approaching clinical trial conduct in low-resource settings with the utilization of CAS, additional insight is provided through enabling the design to view the system holistically and equip researchers with tools that enables them to embrace the non-linearity and adapt effectively. Specifically, understanding clinical trials in this way allows for the identification of patterns that influence the emergence of the system and subsequently ways to address traditional components of research considered outside of research team control.

The community system has social networks, trial information sessions, family dynamics, employment, rumours, and a health system that lead to continual evolution of the CAS (van den Berg et al., 2019a, p.). The trial system is operating within its own set of rules guided by sponsors, eligibility criteria, trial protocols, participants, Good Clinical Practice (GCP) guidelines, and payment terms. These two systems are also open, and thereby constantly in exchange with the external physical environment that carries with it influences from media, scientific progress, research studies, disease, ethics committees, and routine vaccination programs (figure 1). Between the community and trial, a significant power discrepancy is present, indicating which actors have a greater influence on CAS emergence. Each of these aspects was touched upon during the interviews and support CAS theory as a useful model for vaccine clinical trial research in low-resource settings. Therefore, approaching community relations during clinical trials in low-resource settings with implicit linear and mechanistic assumptions will see inconsistent outcomes.

In contrast, we have found that clinical trials within communities is a deeply iterative process, dependent on feedback loops and the interaction of dynamic networks.

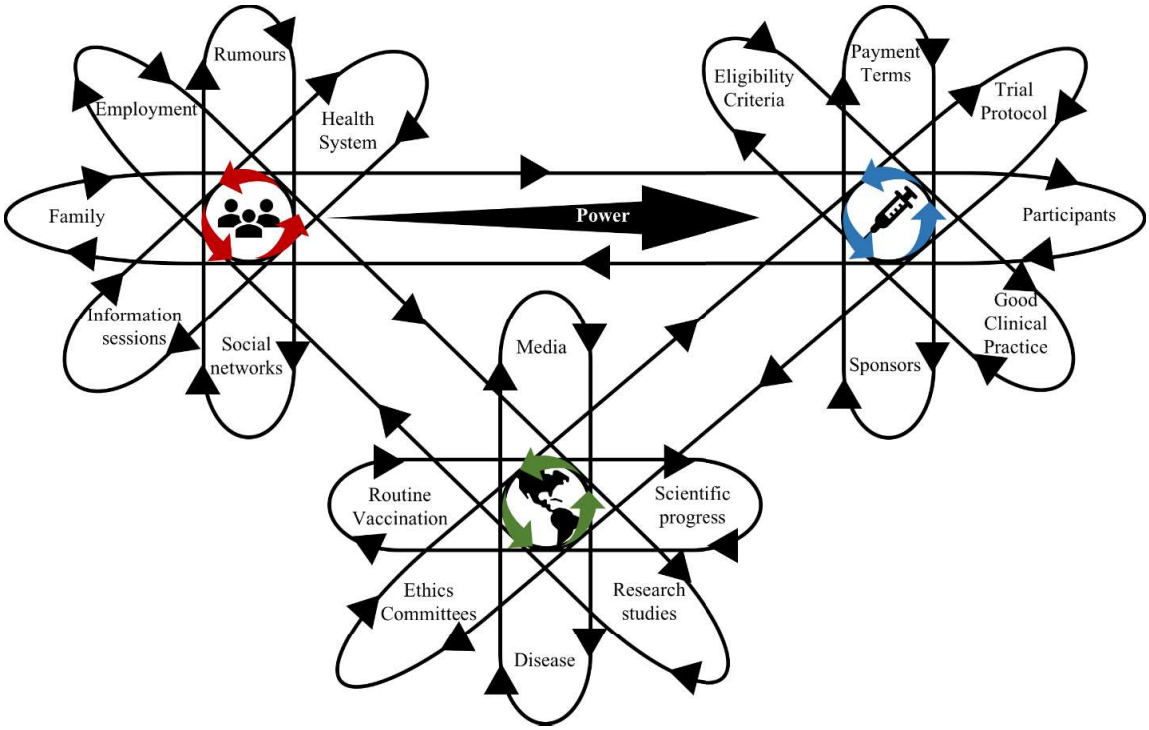

Figure 1. Complexity theory modeling a community system (red), clinical trial system (blue) and the external environment (green) merging into a new iterative system. The identified factors operate within feedback loops and demonstrate an interconnectedness with each actor. The solid arrow indicates the directional weight of power in the system, which is significantly greater on the side of the clinical trial.

In this study the phase III malaria vaccine clinical trial was used as a case study to understand the consequences of two CAS merging and the prospective considerations of relevance for research teams working within this newly merged CAS. Figure 1 models the identified actors and the factors at play in shaping the behaviour of the system. Currently, clinical trials are designed with the assumption that the clinical trial system and the community system operate in isolation. However, the findings of our case study indicate that the emerging behaviour of the system contradicts this

assumption. Therefore, denying the interconnectedness of the community and trial is detrimental to the success of the trial as it does not allow teams to adapt to unpredictable system behaviour. We found that challenges concerning rumours, community scepticism of a new vaccine, employing community members, minor events with unforeseen consequences and hierarchal structures are all behavioural indicators of one interconnected CAS. This CAS operatives with cyclical iterative feedback loops (figure 1) and requires researchers to respond in a similar iterative manner to these challenges. For the research team in this case study, a certain amount of iteration occurred informally and was needed for the trial to proceed in response to these challenges. Below we describe the emerging behavior of the system upon the merging of a clinical trial with a community. In particular the challenges identified by the researchers when carrying out a transnational clinical trial, adhering to standardized clinical trial regulations, while attempting to adapt to the non-linearity of the new system.

One of the main challenges reported by researchers is the difficulty in addressing misconceptions and preventing the spread of rumours, a concern frequently described in clinical trial research (P. W. Geissler & Pool, 2006; Kingori et al., 2010). Our respondents identified community concerns that highlighted commonly reported suspicions around blood, infertility and death in relation to the clinical trial (Fairhead, Leach, & Small, 2006; P. W. Geissler & Pool, 2006; P. Wenzel Geissler, 2005; Kingori et al., 2010; Mitchell, Nakamanya, Kamali, & Whitworth, 2002). As this is commonly reported during clinical trial research in low-resource settings, it is worthy of greater attention during clinical trial design (van den Berg et al., 2019a). Contextual and historical realities influence these rumours and simply providing access to the correct information alone is not sufficient to eliminate them - as they are shaped by the history of community system (P. W. Geissler & Pool, 2006; Obrist et al., 2007). The concatenation of historical events affect CAS and the way in which external factors integrate into the open and dynamic system (Gilchrist, 2000; Luhmann, 1995). Our respondents reported the interplay of social history with clinical trial outcomes and future trust in research, showing that it is insufficient to assume independence of the social system from the clinical trial system.

To adequately address rumours, or better to prevent them, clinical trial design needs to acknowledge the emerging CAS that occurs when researchers enter a community. This extends beyond the initial introduction of the study and into the feedback sessions following the conclusion of the research. This will impact both clinical trial outcomes and future trust in research as rumours can be a reflection of the community's sense of dependence and inequality in relation to the clinical trial, expressed in familiar ways to the community (Enria et al., 2016; P. W. Geissler & Pool, 2006; van den Berg et al., 2019a). A few respondents in our study expressed an awareness of this dependence and inequality. Highlighting the need for more to be done for the communities in which they are working, "*you cannot just collect data and forget about them"*.

The kaleidoscope of feedback loops that are a part of the dynamic interactions within the CAS can make the identification of rumours and their roots difficult, however acknowledging this complexity and its consequences is necessary to strengthen clinical trial design. This can begin by identifying the rules which govern feedback loops related to rumours and to the historical roots out of which they have arisen. This can then be utilized for stronger community relations through communication about the vaccine by targeting these aspects specifically as a research team within the CAS (Essé et al., 2008; Ojakaa et al., 2011).

Beyond historical events which influence the CAS, introducing new and unfamiliar components into a system can also create unpredictable and non-linear outputs in the system. Within CAS, the outcome of an intervention can be major with what seems like a small situational change (Cilliers & Spurrett, 1998; Maguire et al., 2006). Researchers reported the challenge of introducing a new injectable vaccine study into the community, particularly when it is the first clinical trial taking place of this magnitude.

The inherent quality of CAS is unpredictability, in part due to the numerous feedback loops and networks interacting. For instance, the sensitization process around introducing a new vaccine could be further complicated by the presence of external research institutions conducting different studies, as was reported by respondents. The clinical trial is embedded in the social system but

also open to the external environment. These external factors have an influence the CAS and aligns with three attributes that Cilliers (1998) assigns to CAS: *i) complex systems are open systems, ii) complex systems consist of a large number of elements iii) these elements interact dynamically* (Cilliers & Spurrett, 1998). These attributes are also evident in the concerns raised about the introduction of a new HIV vaccine, where they highlight the importance of well-trained staff and a sensitivity to the local variations in vaccination culture (Streefland, 2003a). Other qualitative work in Kenya has also called for a greater emphasis to be placed on the norm sensitivity of health workers providing vaccine, as this is a way of identifying the rules of the CAS and thereby addressing the concerns as there emerge (Ojakaa et al., 2011).

While CAS outcomes are non-linear and dynamic, patterns of interconnections and cultural concepts emerge in each community, which impact the acceptance of a new vaccine (Schaetti et al., 2011; Streefland, 2003a). Work looking at introducing a new human immunodeficiency virus (HIV) vaccine also emphasizes the importance that staff is prepared to adapt to new contextual settings (Streefland, 2003a). Respondents often spoke about the role of local staff who were well-versed in cultural norms as well as the importance that the rest of the research team is aware of the community sociocultural values. Being embedded in the community and viewing it through the lens of complexity theory enables clinical trial researchers to better understand the rules governing the cause and effect within the local context (Sawyer, 2003). However, operating in this way within the community is not without challenges (Chantler et al., 2013). The dispute that respondents described of a staff member losing their employment and subsequently contributing to circulating rumours or a politician using social events to gain support through discrediting the trial can be the consequences of being embedded in the communities in this way. The balancing of the clinical trial domain and everyday community life is challenging and requires a careful mediation that is open and searching (Chantler et al., 2013; P. Wenzel Geissler et al., 2008). Within complexity theory, these reported events are known as the *butterfly effect* where small changes in the initial system have major emerging implications (Capra, Juarrero, Pedro, & Uden, 2009; Holland, 2014). The simple act of a community member losing their job due to not meeting the requirements, had implications on the trial as a whole and resulted in the spread of rumours that impacted the emerging image of the trial – an unpredictable, minor event that created ripples in the larger system as a whole.

The unpredictability and non-linear nature of CAS described above makes clinical trial research in low-resource settings challenging. The social system in which the research is carried out must therefore be integrated into the study design and not simply viewed as a single element of the clinical trial system. In addition to being aware of the cultural values and norms which influence the rules of the CAS, the hierarchy of the system is relevant to these rules as well. CAS are systems that have a hierarchy of power (Gilchrist, 2000). Central to the mediation within communities are the leaders, having a strong influence on the system as a whole. Respondents reported them contributing to the overall acceptance of the trial and also as having the power to create suspicions around blood draws if these hierarchal structures are not respected. Community leaders in Kenya have been identified to use their authoritative power to promote clinical trial acceptance or generate suspicion, depending on their perception of the research team (Angwenyi et al., 2014). Being aware of this hierarchy within the community will support researchers by equipping them with the ability to better understand the rules governing the feedback loops and networks within the community and the emerging patterns.

By integrating the above learnings into community engagement practises, vaccine clinical trial design can better embrace the unpredictability inherent to research in human communities. As the merging of a clinical trial and the community form a CAS, researchers working in any clinical trial that is embedded in a human community need to have the tools to be dynamic and adaptive to local realities. Designing a clinical trial with components of iteration and reflexivity in synergy with the regulatory requirements will equip researchers to better adapt to the emerging behaviour that is inherent to all social clinical trial systems.

CONCLUSION

In this study we have identified the behaviour of a clinical trial system upon the merging with a human community. The factors identified by our respondents, as seen through the lens of complexity theory, are integral to informing how clinical trial research can be tailored to the local social setting. This expands into all clinical trial research operating in human communities.

Prospectively, this pushes clinical trial design to incorporate iterative practices that adapt to the feedback loops and emerging behaviour of the clinical trial.

Here we have identified the key role that complexity theory plays in improving clinical trial design. Further research investigating other clinical trials and geographical settings through the lens of complexity theory is needed. This can build a consensus on specific system behavioural patterns that most heavily require an iterative focus by the clinical trial team. Through the establishment of these patterns a more standardized approach can be used to design iterative steps into any clinical trial.

Abbreviations

CAB	Community Advisory Board
CAS	Complex Adaptive System
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
SU-IRB	Strathmore University IRB

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the local ethics body, Strathmore University IRB (SU-IRB). All participants provided written consent to participate after being informed of the study details.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

This work was funded by the Swiss National Science Foundation (P0ZHP1_172115), the Canadian International Development Research Centre (IDRC) and the Rudolf Geigy Foundation. The funders had no role in the design of this study protocol, in data collection, data analysis and interpretation of the data, or in writing the manuscript.

Authors' contributions

MV and MT conceptualized the paper. MV wrote the first draft. MV, SM analyzed the interview data. SM, BO, NS, NBA and MT reviewed and provided substantial input into the revisions. All authors read and approved the final manuscript.

Funding Sources

This work was funded by the Swiss National Science Foundation (P0ZHP1_172115), the Canadian International Development Research Centre (IDRC) and the Rudolf Geigy Foundation.

Conflicts of Interest

The authors declare no potential conflicts of interest. All authors attest they meet the ICMJE criteria for authorship.

COMMUNITIES AND CLINICAL TRIALS: A CASE STUDY FROM THE RTS,S MALARIA VACCINE TRIALS IN EASTERN AFRICA

Journal: Journal of Empirical Research on Human Research Ethics

Submission date: August 2019

Machteld van den Berg [a,b,c], Bernhards Ogutu[d, e], Nelson K. Sewankambo [f], Sonja Merten[b,c], Nikola Biller-Andorno [a], Marcel Tanner, M.[b,c]

a. Institute of Biomedical Ethics and History of Medicine, University of Zurich Winterthurerstrasse 30, 8006 Zurich, Switzerland

b. Swiss Tropical and Public Health Institute, Socinstrasse 57, 4051 Basel, Switzerland

c. University of Basel, Petersplatz 1, 4001 Basel, Switzerland

d. Kenya Medical Research Institute (KEMRI), Mbagathi Road, Nairobi, Kenya

e.CREATES, Strathmore University (SU), Madaraka Estate, Ole Sangale Road, Nairobi, Kenya.

f. College of Health Sciences, Makerere University, Upper Mulago Hill Road, Kampala, Uganda

ABSTRACT

When clinical trials enter human communities, two complex systems merge – creating challenges for the clinical trial team and the human community. This is of particular relevance for clinical trials in low-resource settings where the resource scarcity can intensify inherent inequities. Complexity theory is a useful lens to better understand and design clinical trials to reduce these inequities. Here we present a case study of a phase III malaria vaccine clinical trial. Through qualitative interviews with researchers and caregivers of pediatric participants we elucidate rules that should shape the emergent behavior of the clinical trial system. Respondents from both groups reported financial and social contextual realities to be major drivers in the system. Specifically, we found a strong historical path dependency in the community that was closely tied to the relationships with researchers and indicative of the structural inequities. We elaborate on these findings and offer recommendations to improve trial design.

INTRODUCTION

Clinical trials in low-resource settings have rigorous ethical, protocol and regulatory requirements to adhere to when conducting their research (van den Berg, Machteld et al., 2019). On the other hand, the research sites where clinical trials take place contain human communities that have webs of complex social networks. The communities are dynamic with changing adaptive community systems which pose challenges for researchers, research participants and other community members to operate within the demands of the formal clinical trial requirements (van den Berg et al., 2019a; van den Berg, Machteld et al., 2019).
The extensive regulatory requirements and complex social networks that make up both the clinical trial and the human community intersect during clinical trials, this leads to an expansion and interconnectivity of actors within the clinical trial system (Montgomery & Pool, 2017). Therefore, upon the initiation of a clinical trial in a low-resource setting, that human community becomes a part of the clinical trial and can be seen as one system (van den Berg, Machteld et al., 2019). Complexity theory is an explanatory framework that can be used to model this new clinical trial system, which provides a conceptual toolbox to best adapt to the non-linear reality of working in human social systems (Sawyer, 2005).

This newly expanded clinical trial system is guided by a set of rules that shape the dominant patterns among the agents in the system, relevant for both the researchers and the community where the research is taking place (van den Berg, Machteld et al., 2019). These simple rules are not classical cognitive and linear rules guiding behavior, instead they describe a collection of patterns that emerge from the system as a result of numerous feedback loops (Gomersall, 2018). Elucidating these simple rules for operating in low-resource settings can enhance ethical clinical trial conduct. Here ethics guidelines that consider the system's complexity can be conducive to clinical trials in low-resource settings. The Council for International Organizations of Medical Sciences (CIOMS) guidelines provide well-reasoned answers to ethical dilemmas in these settings, and further guidelines are not necessarily the answer for better research conduct. However adaptive tools that are responsive to context can support local researchers to adapt to the problem of the unpredictability associated with working in social systems (Gauri & Khaleghian, 2002; Nichter, 1995; Stanton, 2004; Streefland, 2003b; Zimet, Liddon, Rosenthal,

Lazcano-Ponce, & Allen, 2006). Here we aim to complement existing guidelines through providing the tools to gain a thorough understanding of the patterns that emerge and the simple rules guiding behaviour upon the initiation of human research in low-resource settings.

Through understanding the simple rules that guide the clinical trial system, feedback loops and the corresponding emergent iterative behavior can be better predicted (van den Berg, Machteld et al., 2019). We will examine clinical trials in low-resource settings through the lens of complexity theory (Braithwaite et al., 2017; Capra et al., 2009; Holland, 2014; Neely, 2015). First, we will outline the attributes associated with complexity theory and the clinical trial system. Second, we will present our case study focusing on experiences of two main actors, caregivers of participants in a pediatric clinical trial and the researchers conducting the clinical trial in the social community. By presenting the case-study from two different perspectives, we are seeking to provide a balance between the different themes that arise (Mkhwanazi, 2016). And third, we will discuss the simple rules and their implication for future clinical trial design in low-resource settings.

Complexity Theory and Clinical Trials

Clinical trials operating in human communities do not rely exclusively on standard operating procedures (SOPs) to define all details of community engagement. This is due to the complexity of operating in human social systems with numerous interconnected networks. The system adapts over time to its feedback loops and their interactions, making the prediction of its trajectory extremely difficult due to the vastness of the individual elements that make up the system (Braithwaite et al., 2017). Input A will not always lead to output B and can therefore not be predicted in a mechanistic way feasibly detailed by a standard operating procedure. Complexity theory provides a new paradigm of approaching this problem of unpredictability through providing an overarching explanatory framework. Fixed SOPs have a specific aim in a clinical trial and are written to be applied to a broad audience, they are therefore insufficient in predicting the precise behavior of a clinical trial system operating in a human community. Complexity theory can provide a model to promote adaptability and embrace the unpredictability through identifying the more patterned rules that guide the system (Braithwaite et al., 2017).

Complexity theory arose out of an array of different fields simultaneously, ranging from biology to economics to computer science (Holland, 2014). According to complexity theory, complex adaptive systems (CAS) exhibit patterns of non-linearity, unpredictability, openness, interdependence and emergence (Neely, 2015). This non-linearity is a result of the actors within the system adapting to emerging circumstances. As a result, a CAS model will not provide a mechanistic answer detailing the step-by-step design of a clinical trial. It will, however, provide a framework to accept the tensions and paradoxes inherent in clinical trial research and a means to accept the uncertainty (Braithwaite et al., 2017). While linear rules cannot be applied to a CAS, the retrospective identification of simple rules can better predict emergent behaviour.("Simple Rules," n.d.) Complex adaptive system theory is therefore a useful framework to understand both human communities and clinical trials, which become one system upon the initiation of the study (Capra et al., 2009; Gilchrist, 2000; Luhmann, 1995; McDaniel, Driebe, & Lanham, 2013). CAS can be applied as an explanatory model to understand the nature of each system and elucidate the system's actors and rules guiding the behaviour (Neely, 2015; Ramalingam et al., 2008; Sawyer, 2005). This can support clinical trial researchers when responding to unpredictable pressures in an iterative, dynamic and interdependent manner (Khan et al., 2018).

Presently, clinical trial design assumes that the clinical trial and the human communities in which they operate function as independent systems. Through approaching clinical trial design that views the two systems more holistically, we propose that less conflicting situations will arise, and the human community and research team can have a more synergistic relationship in the context of the clinical trial.

To further detail this we will look at the human community and clinical trial through the lens of complexity theory. Research traditionally looks at community engagement as a tool to strengthen recruitment and retention in research studies (Johnson, Joosten, Wilkins, & Shibao, 2015). However, clinical trials embedded in human communities have more complex realities that extend beyond these components (van den Berg et al., 2019b). The formation of an expanded CAS upon the initiation of a clinical trial has implications for the community and for the

researchers. To understand these implications, it is important to explore the clinical trial system from the perspective of both the research team and the human community where the participants live beyond enrollment and retention numbers.(Mkhwanazi, 2016) In line with this, we have conducted a case study of a phase III clinical trial operating in low-resource settings.

Case Study: RTS,S Malaria Vaccine Phase III Clinical Trial

The case study looks at a phase III pediatric malaria vaccine clinical trial. This trial is multi-national and must adhere to stringent regulatory demands consistently across diverse health care systems and social systems.(RTS,S Clinical Trials Partnership, 2015b) Here we investigate the participant experience in Tanzania and Kenya, as well as the experience of the research team in Kenya. This clinical trial is now being extended in Kenya into a pilot implementation with the clinical trial team continuing to operate in the community.(WHO, 2018a) This provides a unique opportunity for continued monitoring of the emerging clinical trial system and the implications the trial and the human community have on one another. The findings will inform future clinical trial research design in low-resource settings and provide insight into a viable path towards improving the conduct of these trials in diverse human communities.

METHODS

Study Design

The expanded study design and methodology have been described earlier (van den Berg et al., 2019a; van den Berg, Machteld et al., 2019). To understand the priorities and experiences of both the clinical trial researchers and the human communities where the pediatric participants live, we conducted a series of in-depth interviews with members of the RTS,S research team and parents of participants in the RTS,S phase III clinical trial. RTS,S malaria vaccine phase III clinical trial took place between 2009-2014. It was carried out in 7 African countries and 11 clinical trial centres (RTS,S Clinical Trials Partnership, 2015b). We selected participants from three clinical trial centres in Tanzania and Kenya, and members of the research team from two clinical trial centres in Kenya. These sites were chosen due to their geographical proximity, but different health and social systems.

In-depth Interviews

Interviews with parents were held in the home of the participants. Interviews with the researchers were held at the research site of the clinical trial. All interviews were held between March 2017 and March 2018. Respondents were selected based on their participation in the phase III RTS,S malaria vaccine clinical trial. Interviews with caregivers of participants were conducted together with local, bilingual research assistants and the first author. Interviews with researchers were conducted by the first author in English.

Data Analysis

Interviews with parents of participants were recorded, transcribed verbatim and then translated to English. Interviews with researchers were recorded and transcribed verbatim. Analysis was initiated immediately following the interviews and MAXQDA software was used for line-by-line microanalysis of the interviews, followed by thematic coding. All coding was done by MV and selected parts of the coding was reviewed by SM. The focus of the analysis was on the changes in the community upon the initiation of the RTS,S clinical trial, the relational dynamics between

researcher and community, and the perspective of both the researcher and the community on the clinical trial.

Ethics

Informed consent was obtained before each interview was conducted. The recorded audio, transcripts and participant information were stored separately in password protected files. All interviews were anonymized.

Ethical approval for the study was obtained in Tanzania (i) from the National Health Research Coordination Committee of the National Institute for Medical Research (NIMR) through the Tanzania Commission for Science and Technology (COSTECH) and Ifakara Health Institute IRB (IHI-IRB), and in Kenya (ii) from Strathmore University IRB (SU-IRB).

RESULTS

The results presented here relate to other work in the context of a larger project (van den Berg et al., 2019a; van den Berg, Machteld et al., 2019). There were a total of 55 in-depth interviews with parents of participants in the three selected sites as follows: Tanzania (n=18), Site 1 in Kenya (n=20) and site 2 in Kenya (n=17). The average interview lasted about 29 minutes, with the longest being 45 minutes and the shortest 20 minutes. The duration of 7 interviews could not be included due to logistical constraints as the original audio files were erased after transcription. There were 11 interviews with the researchers and each lasted on average 53 minutes, with the longest being 2 hours and the shortest 28 minutes.

During our interviews the complexity of the clinical trial system was repeatedly identified. In particular it was reported by the researchers that the clinical trial system is non-linear and requires adaptation to each unique context. This is illustrated by the quote below from a researcher describing their experience in the community as a clinical trial researcher:

> *Researcher 11 It is not a straight line that will be smooth all the time. You may have challenges that will be different with every study.*

Drawing on this non-linearity, we identified recurrent themes in both groups of respondents. The factors driving the emerging behaviour of the clinical trial system that were frequently reported were blood draws, participation benefits, community influencers, finances, communication and health. There was a strong overlap between the two groups of respondents in themes identified. However, the caregivers reported more concern with the financial and health contexts. The researchers had a greater emphasis on the consequences of communication and the relationships built during the conduct of research in a community. Both placed a heavy emphasis on blood draws and the role they played in the clinical trial system. Here we present these themes with quotes from both groups of respondents to illustrate the findings.

Blood draws

Almost all caregivers and researchers in Kenya reported concerns raised by the community concerning blood draws. In Tanzania it was raised less often as a concern although they identified this, along with the associated rumours, as the leading issue in the clinical trial. It affected community perception, relationships with the researchers and trial enrollment.

> Researcher 08*: The main issue in the community is about blood samples that we take. People want to know "what are you doing with the blood?" someone could be on the road and tell you "I heard you people are doing research and you are collecting blood samples". This is someone who is not participating but is part of the community and they want to know what you are doing with the blood.*

> Caregiver 32*: Excess blood draw was done where the vaccine was administered. People ran away because of the excess blood draws.*

During interviews the caregivers in Kenya reported the term "*Logo rembji"* meaning "*taking people's blood in excess*". It was reported to be associated with members of the research team. Respondents described that some community members suspect researchers of entering the community, enrolling participants in research, withdrawing the blood and draining it without their consent. It is then suspected of being sold or used for satanic purposes. In the context of this pediatric trial, it led to the suspicion that the children enrolled will get sick and then not respond to treatment in the hospital.

> Caregiver 01*: Sometimes when someone came like the way you have come now, then someone just tells you that "No! No! No! I don't want a researcher near me! No! A research person will 'Logo rembji' I don't want them".*

> Caregiver 19: *People are saying that some people have given their children's blood which is being taken to the devil. The devil takes their blood. But they say a lot of things and they can't agree up to date.*

Benefits

The benefits associated with participating in research, specifically the free medical care and transportation to the research facility, had a powerful impact on the clinical trial and how the community responded to it. Researchers identified this and linked it to how it strengthened the relationship with the community and the community engagement that is also outlined in the trial protocol.

> Researcher 03: *The community feels that at least the researchers don't just come and get our blood, do their research and go away. At least there is not only community engagement, but also a benefit to the community in several ways.*

Both groups of respondents identified the influence that benefits had in building a rapport with one another. Furthermore, almost all respondents emphasized the impact played by the manner in which the benefits were provided. When the participants and their caregivers were treated warmly and with respect, this had a significant impact on the experience that the community members had with the clinical trial.

> Caregiver 33*: What I would say is that they took good care of us, accorded respect, there was good rapport, the study staff would welcome us warmly as we were part of them. We would be welcomed more warmly in the study than the government clinics. We were delighted in the way they handled us.*

Influencers and gatekeepers

There are a number of actors in the clinical trial system that respondents identified as having more influence on the clinical trial system than others. In particular, mothers-in-law were often singled out as being opposed to or supportive of the research and depending on their position, the grandchild would or would not be enrolled. This was the case even when the mother was the primary caregiver and the individual formally consenting.

> Researcher 08: *In some cases, you would find that the mothers-in-law had a lot of say on if the participant is going to participate in the study. In some cases we*

would find that someone would decide to withdraw but the reason they withdraw is because they were influenced by the mother-in-law. We find the religious background and the mother-in-law probably don't accommodate some of the things that they felt we were doing. So I would say that in this area, in some cases, you would find that the mother in laws or even other people who are not the parents, had say on whether those people would participate.

Caregiver 25: *I was not ready stating to my mother-in-law that the research is known to draw a lot of blood from children. My mother in law encouraged me, saying that the child will benefit a lot not only against malaria but against all other diseases that may come up. They came back, and I allowed my child to be enrolled into the study.*

Relationships

Frequently it was highlighted by respondents that having a relationship with one another as human beings was a large part of the trial. This was emphasized consistently by caregivers as being positive and it made the research more easily accepted in the community.

Caregiver 47*: They were humble and they loved children, that is the uniqueness*.

Researcher 02: *Don't treat them as a subject, treat them as someone who has sacrificed their time who has put aside some of the things they were supposed to do to come to the research centre.*

The researchers identified the role that relationships with participants and their families played in many aspects of the trial. Including enrollment, retention, adherence to scheduled visits and minimizing rumours. However, there were also drawbacks for the researchers when they became emotionally involved, in particular when a participant became critically ill and died during the clinical trial. This was an emotional burden and required the researcher to grapple with the multiple roles they have as a member of the research team and also an individual deeply embedded in the community due to the research.

> Researcher 11: *When you go home and sit and you now analyze how it was in the day, and it is like, surely did I help that family? Did I help? It haunts you if you did not really do well. It makes you feel bad. You want to get them the next day to see how they are. Because once in a while a participant died and when the participant dies you want to console them. It is difficult as a person, as a human, as a mother. You also have your job and there are many dynamics.*

Finances

Participation in the trial was often identified by caregivers to be linked to their lack of financial resources. This was a strong factor in the clinical trial system, encouraging participation in the research as the free medical care relieved a financial burden when the child would fall sick. From the researcher's perspective, alleviating the financial burden in this way was framed as conducive to community engagement as it brought the researcher into deeper relationship with the community.

> Caregiver 35*: The people were enrolled praised the study. Most of them are the people who come from around who earn a little money. Sometimes when the child falls sick it becomes difficult especially for us who are farmers.*

> *Researcher 02: Another thing that motivates them to come, is the transport reimbursement and paying for inconvenience. You also pay for that time, so these are mothers who would not go to the farm that day, these are mothers who would have gone to the market to sell their produce but they are spending their day at the facility. So try to compensate that way, they feel like you are thinking about them, you are thinking about the time they are spending with you.*

The clinical trial alleviated the financial burden, when it ended it created tensions when other children could not receive the same benefits as past participants. The caregivers were still subject to the structural inequities and had to once again use their money to pay for the care when their children fell sick.

Caregiver 13*: The researchers have left us but I still need them.*

Caregiver 21: *I didn't want it to end, it's the ending of the study that I didn't like. I just want the children to continue with it.*

This created moral distress in the researchers, to the point where they reported using their personal money to finance needed medicines for children from the community.

Researcher 11: *Once in a while I can even take them, have the clinician prescribe and I buy drugs for them on the clinics outside. Sometimes I just ask the clinician to check, then whatever they have prescribed I can walk across, you know outside the gate, to the pharmacy and buy for them.*

Communication

The role that communication played in building trust was highlighted in most interviews, from both groups of respondents. It was identified to be the foundation on the which the engagement with the community was built. Communication was a factor in the trial system that reduced the spread of rumours, strengthened understanding, protected the integrity of the data and a sense of trust between the two groups of respondents.

Caregiver 19: *The researcher who came to me talked very well with me. She taught me and explained that even if people are talking that way, it's not that way. She talked to me very well and I agreed.*

Researcher 09*: The minute we don't give the right information, the minute there is no trust, then it means even the investigators will not trust on the information that is being generated. And that will affect data. So it can affect the data and also our trust in the community and maybe future interactions with the community.*

The caregivers also identified instances where communication between the research team and themselves failed. For instance clarifying the terms of the consent and the timeline of the study. This then affected the overall way in which research was perceived by the community and thereby future interactions.

Caregiver *29: Towards the end of the study, the study developed a weird behavior. They would ask the reason for your going to the clinic. You would be discouraged and wonder why they behaved in such a manner - not being treated with respect. The doctor would take more time before attending to you. I didn't like that. I like that after people consent to do something, they do it from beginning to the end.*

Health

The health and well-being of the pediatric participants was a priority for all of the respondents. This is related to the financial burden above, as caregivers in poverty struggled to access medical care for their children in the absence of a clinical trial. Having the possibility to deliver needed clinical care provided relational motivation for the researchers and fulfillment in their work. It created trust between the caregivers and the researchers, which spread into the community.

Researcher 02: *It was fulfilling, most of the mothers were happy in the trial. Their reasons being their children had access to medical care, without the trial they would not have access to the medical care. During the vaccine study, whenever their children felt sick irrespective of the condition, we would offer them care. So those children who had road accidents or trauma injury would have their bone fixed and surgeries were done so they were happy that they benefited, their health improved and they were willing to come back.*

Caretaker 40*: I knew my child will get better treatment and medication. Before the trial we were given a bottle of medicine and had to share it with four people but when I joined the trial I was getting a bottle and could open it when I got home.*

Researcher 09*: The fact that we saved many lives was motivating both for us and the community as a whole.*

Caretaker 25*: I didn't experience any negative side of the research. It was all goodness. I received aid from January, receiving free medication for my child*

until the end of the year. I just said thanks to the research team. I still have young children wondering when again they will be enrolled into a study so that I benefit as I had benefited from the past.

Providing medical care for participants generated a positive relationship between researchers and the community. However, in serious cases when a child not eligible for the clinical trial fell ill the caregiver would come to the clinical trial centre needing medical attention – this would create challenges for the research team. As the researchers have to balance their accountability to the sponsor with their role in the community and have limited financial resources.

Researcher 11: *We told them we will only treat the participant and the budget is so stringent that it can only treat the volunteer. We don't want to have extra patients, you see. We budget strictly according to the demands of the study because of finances and sponsor. So if you open the door everybody will come. But if you do not treat and you refer them to the government facility and they eventually die and they are not in the study, then you are in trouble in that village. You can't even attend that funeral because you neglected them. And even in the future if you go recruiting for another study, adult or whatever, in that village they will tell you "no last time you refused to help our child and the grave is there, you can look at the grave" Then you really feel funny. So you really must be very careful. You may go an extra mile and treat and tell them, in the future do not bring because we are not allowed to do this.*

Simple Rules

The main factors influencing the clinical trial outcome highlighted by both the researchers and caregivers have been listed in Table 1. The corresponding simple rule has been developed based on the qualitative analysis of the main themes and relevant literature to the contextual setting. The respondents described emergent behavior of the clinical system and the ways in which the trial design best supports harmonious relationship between the researchers, the caregivers and their communities.

Factor	Simple rule	Application for trial design
Past Research Experiences	The human community has a historical path dependency. *Heavily context dependent*.	Map historic context and integrate into the clinical trial design to harmonize different perspectives.
Participant Benefits	Balanced benefit-sharing between participants and the research team reflects mutual respect and harmony in the clinical trial system.	Build a relationship where each group gets what is required and can contribute where their expertise lies.
Social Influencers	Family and community members have opinions that influence enrollment and the acceptability of participation in the clinical trial.	Identify the whole system and its parts. See where factors and actors are interconnected and recognize the interaction needed to shape the behavior.
Relationships between trial actors	Human relationship plays a major role in system emergence.	Identify how positive emotions and social norms of reciprocity drive adaptive capacity in the clinical trial system.
Economic Context	The economic context influences informed consent practices and also the moral distress of researchers. *Heavily context dependent.*	Recognize the economic context of the clinical trial system and provide flexible options for researchers operating in the system.
Quality of Communication	Ongoing, transparent communication leads to a positive perception of research in the community.	Design a communication strategy that is sensitive to the other factors identified relevant to the system and apply it in an iterative, transparent fashion.
Access to health care services	Good child health is a priority for all identified actors in the system.	Enable researchers to provide care on humanitarian grounds for critical cases.

Table 1. *Factors identified by caregivers of pediatric participants and researchers conducting the clinical trial as shaping the clinical trial system.*

DISCUSSION AND RELEVANCE

There were significant overlaps in both groups of respondents on the identification of factors that impact the clinical trial system. This alignment is likely indicative of the setting and the five years that the clinical trial operated in these communities. These results provide new insight into the implications of clinical trial systems merging with human social communities. Based on the factors identified by both groups, engaging with the community has large implications that extend beyond strengthening recruitment numbers in the clinical trial. The simple rules highlighted above shows the extent of the relationship between the trial and the community, as well as the ways in which these can be integrated into clinical trial design.

The simple rules highlighted in Table 1 are developed to encourage participatory exchange between the various actors in the clinical trial system. It is important to clarify that the simple rules do not predetermine the exact emergent behavior of the system, as each situation and context is different. Instead this map of simple rules is intended to be used as a supplementary tool that researchers can use to interact with communities in an iterative manner to complement existing ethics guidelines like CIOMS and regulatory requirements such as those described in SOPs. Standard practices in clinical trials focus on protecting autonomy and ensuring consent is free and informed. However, this is challenging in low-resource settings where structural inequities may impede free choice due to a lack of viable medical options outside of the trial. (Kingori, 2015). Through the use of the proposed rules, clinical trials can understand these contextual realities and respond by working with local leadership to generate medical options if necessary.

While there was an overlap in the identification of factors, each group weighed the influence of these factors on the system's processes differently. The caregivers spoke more frequently about the financial burden they as caregivers carry and how it was alleviated by the free health care provided by the clinical trial. Similar results have been reported by other research in these settings (Haire & Ogundokun, 2014; Paré Toe et al., 2013). The researchers viewed communication and human relationships as key factors in the emergence of the clinical trial system. Both placed a similar emphasis on blood draws and the surrounding suspicions.

The difficulties surrounding blood draws in Kenya and Tanzania have been identified elsewhere (P. Wenzel Geissler, 2005; Vallely et al., 2007). The concerns around blood draws are rooted in real historical experiences with research and exploitation (P. W. Geissler & Pool, 2006; Graboyes, 2015). Through the lens of CAS theory, these experiences are indicative of a historical path dependency exhibited by the system – where past research experiences influence the present state of the system. The ways in which the hesitancy surrounding blood draws were reported by the caregiver and researcher was different. The caregivers experience pressure from the community and family to avoid research due to this, which was expressed as concern for the welfare of the child. Furthermore, often the caregivers themselves have concerns about the impact that the lost blood will have on the child's health. The researchers described concern about blood draws as a lack of education and cognitive understanding on behalf of the community and caregiver. This is also related to historical myths of those who move around the community and night accosting people and draining their blood for sale or cultic rituals. This disconnect, if unaddressed, can lead to further skepticism and affect the clinical trial from moving forward successfully (Kingori et al., 2010). In clinical trial design, this can be addressed by identifying the historical path dependency of the human community a research team is working in. For instance, participatory techniques to promote an understanding of the community research experiences and appreciation of what happens to blood that is taken from a participant have been successful in microbicide clinical trials in Tanzania (Vallely et al., 2007).

The interrelatedness between factors was also evident. For example, finances and health care exhibited a dependent pattern with one another. The more a caregiver spoke about finances, the more they also reported valuing the health care provided. The relational factor and social influencers also displayed significant interrelatedness, from relying on members of the research team with strong relational skills to identify the social influencers in the community to the importance of relational skills with regards to factors such as communication and benefits. Valuing human relationships and having strong relational skills as a researcher was reported to be important for communicating clearly with the caregivers. And in both Tanzania and Kenya, caregivers valued the relational skills of the researchers when they provided quality care. Caregivers highlighted how they valued a researcher who made them, and their children feel

comfortable and clarify the kinds of benefit expectations they should have from the research project. Inversely this was true too, in cases where respondents reported being disappointed by the project, it was frequently a result of a disconnect due to poor communication skills around the kinds of benefits participants and caregivers expect from the study.

This difference also brings us to the ways in which each group weighed the factors that dictate the emerging patterns of the clinical trial system. Each is rooted in the contextual reality that they inhabit, but this is particularly true for the historical and financial factors. The caregivers are living in a low-resource setting and view the research study as the high-capital resource that can alleviate the burden they face when a child is sick, which is central to their life. The researchers are predominantly speaking from the historical experience in the context of their professional role during the qualitative interviews. They therefore identify their contextual experiences where communication was transparent and successful as being the main driver of clinical trial system emergence. Speaking from their role as a clinical researcher, they expressed their relational fulfillment in providing medical care and healing the participants in need of medical attention, central to their professional ethic. To be able to adapt to the contextual differences, clinical trial design needs to encourage research teams to work with communities in an iterative fashion. This is of particular relevance when the clinical trial site hosts numerous trials over a longer period of time, encouraging ongoing and adaptive interaction. Each of these factors and simple rules influence feedback loops within the system, which vary depending on the context. The interrelatedness identified showcases the importance of a wholistic approach, paying careful attention not to negate different perspectives across roles (researcher and caregiver).

Transnational clinical trials in low-resource settings have unique challenges, many of which fall on the shoulders of the local researchers (Crane, 2010; Merritt, Taylor, & Mullany, 2010). Researchers reported this struggle, with one expressing "*it is difficult as a person, as a human, as a mother*" when speaking about the conflicting duties towards the community, the research institution and the social relationship. The capital discrepancy in low-resource settings between the clinical trial and the community often has researchers facing a moral dilemma. In this case study, it led to the use of their personal finances to support caregivers when seeking medical care

and distress when faced with professional obligations that were not socially accepted in the community.

Through designing clinical trials that operate in local communities, using CAS as a framework to better predict the unique system emergence, some of the burden on researchers can be alleviated. This will mean equipping research teams with the possibility to operate in iteration with reflexivity, adapting to the local setting and progression of feedback loops in the system. Ethics committees can support this by acknowledging the non-linearity of the process, promoting the identification of the feedback loops and application of these simple rules to clinical trial design preemptively. Simple rules that are designed around research experiences, benefits, social influencers, relationships, finances, communication and health care must be incorporated from the start of the clinical trial in the community, when the system forms a new CAS. When the project initiates, the identification of the interrelatedness between these factors it will also help researchers fine-tune the iterative process to their local context. These factors should be considered by researchers at the beginning of the trial and applied based on their relevance for that contextual setting - enabling researchers to better respond to the non-linear nature of applying clinical trial requirements in human communities.

CONCLUSION

This study elucidates that the implementation of a clinical trial is heavily influenced by the complexity and unpredictability of the human social system, which thus makes it difficult to implement procedural and ethical requirements which do not give room to respond to the highlighted implementation challenges. Supplementing regulatory requirements with clinical trial design that encourages iterative processes can address some of these implementation challenges. For example, allotting time for the clinical trial team to meet and discuss the iterative process and make amendments to the process as necessary. The simple rules highlighted here should be used as a tool to guide exchanges between actors in the clinical trial system and inform the design of the clinical trial. Future research should establish the use of these simple rules across different contexts and assess the impact of integrating them into the design on clinical trial experiences in local communities.

GENERAL DISCUSSION

Overview

In this section I highlight the findings from the papers and explore the ethical implications of the results from the compiled empirical data. Drawing on my findings, I conclude that clinical trials are complex adaptive systems that need to be sensitive to the contextual realities of the human communities within the system and subsequently describe how to integrate this into clinical trial design. I will begin by exploring these realities, for both the caregivers and human participants and then the researchers on the frontline of the clinical trial. Then I will discuss the role of relational ethics in supporting frontline researchers and enhancing caregiver agency. And finally, I will then discuss the limitations of the study design and areas of future research.

CONSENT AND CHOICE

From the empirical paper, *Clinical trials in low-resource settings: the perspectives of caregivers of paediatric participants from Uganda, Tanzania and Kenya,* the provision of medical care created, at times, an undue inducement. What was exceptionally evident during the systematic analysis of the qualitative data was the frequency with which caregivers spoke about their participation in relation to their gratitude for free medical care provided by the trial. This extended into community decision-making and acceptance around the presence of the trial, as discussed in the paper. The low-resource context has been shown to influence the ways that risk is interpreted by those consenting to participation in research (Cottingham & Fisher, 2016; Walker et al., 2018). The use of a framework for the analysis was intended to capture this context and understand the multidimensionality of the embodied caregiver.

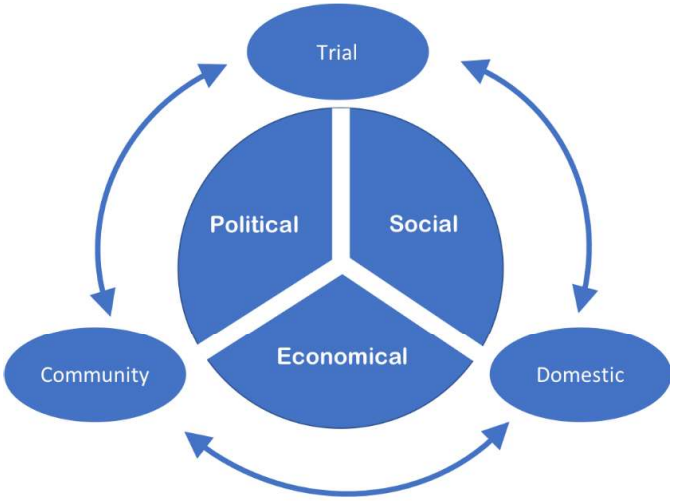

Figure 1. Framework for analysis outlining the interplay between community, domestic and trial contexts that the respondent inhabits and the economic, political and social realities of the embodied respondent.

By understanding the caregiver from the social, economic and political context - choice can be better understood and its interplay between the different realities that a caregiver and participant inhabit. I learned through the interviews that each reality has a significant impact, as is highlighted in *Clinical trials in low-resource settings: the perspectives of caregivers of*

paediatric participants from Uganda, Tanzania and Kenya, however the economic state of many caregivers resulted in the negation of risk when caregivers were offered free medical care.

From this, it is possible to conclude that the provision of medical care can significantly hamper choice and caregiver autonomy. This has been raised as a challenge in research with human participants in low-resource settings when the services offered by the institution far surpass the local health services (Mtove et al., 2018; H. T. Shapiro & Meslin, 2001). Others have even argued that the decision to participate in research has been made before the risks have been clarified during the consent process (Paré Toe et al., 2013). This brings forth difficult questions concerning autonomy when the only means for caregivers to provide needed health services to their child is a clinical trial.

Should we do research when choice is diminished?

I began this thesis framing my questions around the foundational bioethical principles and here I will come back to that. Specifically, looking at the role of autonomy and its relevance to choice and informed consent with regards to the understanding of risks and benefits of research participation in low-resource-settings. One of the aspects I raised in the introduction was the differences between the social systems, where individual autonomy reigns in Western countries, there is a greater focus on the collective social system in the low-resource settings studied. It has been argued that the emphasis in clinical trials on individual choice neglects the different social and structural contexts that are common in low-resource settings (Gikonyo et al., 2008; Kingori, 2015; Molyneux, Peshu, & Marsh, 2004). Through my interviews I also encountered the prominence of collective decision making and the role of extended families to be very different from the Western values I am accustomed to. Therefore, first I will consider these differences and what that means for choice.

Through my interviews with the caregivers, there was often the theme about the role of their extended families, neighbours and community leader in their decision making. And as I

raise in the paper, *Clinical trials in low-resource settings: the perspectives of caregivers of paediatric participants from Uganda, Tanzania and Kenya,* this is an important aspect of community acceptance of the research taking place and strengthening trust between researchers and the community members. Therefore there must be extra care paid to community engagement practices that extend beyond the individual caregiver to ensure that the correct information is reaching all for those involved in the collective decision making, this can foster autonomy in a setting where the locus of decision making is communal without compromising the principle of informed consent (IJsselmuiden & Faden, 1992).

Another consideration I deem to be even more pertinent to choice, based on my qualitative data, is the glaring structural disparity between the clinical trial health services and those accessible to caregivers outside of the trial. This is a key dimension when it comes to assessing autonomy and informed consent (Kingori, 2015; Mtove et al., 2018; Paré Toe et al., 2013; H. T. Shapiro & Meslin, 2001). As many caregivers in this project discussed their decision to enroll in the trial, they spoke of having a sick child and no money to provide medication or having access to the required services to treat the child. In some cases, this was the moment they decided to enroll in the trial. Having to consent to research without alternative options has been termed the 'empty choice' (Kingori, 2015). What I found through the interviews is in line with what others have discovered, having an ill child makes the caregiver more likely to consent to the research and this raises some red flags and demands further reflection on the role of the trial in our setting, East Africa, and the duties of the trial in relation to these structural inequities (H. R. Fisher et al., 2011).

Implementing a clinical trial in these settings may not remove autonomy, instead I think that drawing the link between free medical care and the absence of autonomy is an over-simplification. Autonomy is certainly restricted, however this existed in a temporal space before the action of medical research and when a child falls sick the consequences are witnessed with or without the presence of a clinical trial. The caregiver's will to keep the child healthy is there, however the only existing choice to do so may be enrollment in the clinical trial. Therefore, autonomy is profoundly limited as a result of these perverse structural inequities that frame the

parameters of choice in everyday life for those living in severe poverty – something referred to as structural coercion (Farmer, 2004b, 2004a). In our study the research does not remove agency, structural disparity does. Paul Farmer frames this accurately when speaking of inequities in low-resource settings:

> *"Their sickness is a result of structural violence: neither culture nor pure individual will is at fault; rather, historically given (and often economically driven) processes and forces conspire to constrain individual agency. Structural violence is visited upon all those whose social status denies them access to the fruits of scientific and social progress." (Farmer, 2001)*

A conflict of principles

Taking into consideration the structural disparity in these settings, we must also consider the consequence of not conducting research, choosing not to act is also action and further denying those with the highest need "*the fruits of scientific and social progress"*(Farmer, 2001). As described by Eisenberg "*impeding medical research no less than performing it, has ethical consequences*" (Eisenberg, 1977). Not conducting the medical research to develop a malaria vaccine (or another therapeutic targeting populations in low-resource settings) would allow hundreds of thousands of preventable deaths to take place while the resources are available to develop a preventative or curative tool. This consequence of inaction would further the "10/90 research gap", a term coined in the 1990s to reflect that 10% of global research potential is devoted to conditions which make up 90% of the global burden of disease (Global Forum for Health Research Organization, 2004). A less severe form of inaction, conducting the clinical trial but not providing medical care, would allow the suffering and preventable deaths to continue in these settings. In the case of the PMVT, the provision of care significantly reduced overall child mortality - with one of clinical trial sites in Kenya reporting a 70% reduction in mortality (Hamel et al., 2014). Therefore, providing medical care and saving lives is a way participants can receive immediate benefits from the research participation and may not necessarily constitute undue inducement (Haire & Ogundokun, 2014). While the preventable

death of a single child is horrendous, this reduction in childhood mortality is a benevolent act by the clinical trial – introducing us to the strings of an intricate web that accompanies ethical deliberation between the principle of beneficence and the principle of autonomy. Determining the ethical course of action means to weigh and balance these ethical principles and then to substantiate this action through supportive moral reasoning.

While there are concerns around autonomy during the conduct of trials in these settings, the beneficence associated with conducting the research may outweigh this inherent limitation on autonomy. Consider this same situation of child mortality in a developed country, if we would be experiencing this volume of preventable deaths in the Swiss countryside we would immediately mobilize and fund this research even if participation in the research was not fully autonomous for the children. Perhaps there is no moral distinction between the imperative to act, only a spatial one. Performing clinical trial research in low-resource settings has ethical challenges as it is difficult to restore autonomy in a setting where the structural violence is such that autonomy is frequently stripped away. But not conducting the research and not acting allows for the disease burden to be remain.

With a pragmatic aim of better health and well-being, we are seeking the *summon bonum,* highest good, and must therefore uphold the foundational principles of biomedical ethics. Through the conduct of clinical trials in low-resource settings targeting diseases endemic to those regions we are on such a path, yet the upholding the principle of autonomy is arguably the most challenging in this task. To develop a justifiable conclusion, we need to discuss how to protect autonomy. According to individual centered rule-utilitarianism "*over himself, over his own body and mind, the individual is sovereign"*(Mill, 1859) which emphasized the principle of autonomy and its role in moral theory, the greatest good should be pursued while concurrently upholding autonomy. This notion in the context of utilitarianism is a narrow perspective on autonomy and to supplement it we must understand the role the clinical trial stakeholders can have in protecting autonomy.

How to address diminished choice?

While the aspiration to remove structural disparity from our world is a worthwhile one, to demand the clinical trial to remedy global injustice before conducting research is an over-extended expectation that will have an inhibitory effect on research benefiting vulnerable populations. Nevertheless, clinical trials operating in these settings do have an ethical obligation to prevent exploitation in their research settings. Victims of structural disparity are certainly vulnerable and vulnerable populations are at risk of exploitation (Macklin, 2003). Proposing to reinstate autonomy by addressing the *lack of knowledge* ignores this vulnerability and instead diverts attention away from the *lack of options* which is underpinning the restriction of autonomy. As our qualitative interviews indicate, caregivers without medical access and sick children have sufficient knowledge to know that enrolling in the trial is their only viable option to ensure the survival of their child. Their decision is not based on a lack of will or knowledge, it is based on a lack of choice. Thus, while the clinical trial is not responsible for rectifying global structural inequity, the lack of local medical infrastructure cannot be separated from the research. Due to this inextricability there is an ethical duty to address this structural inequity as it leaves participants and caregivers vulnerable to exploitation. To address structural inequity the clinical trial must address the lack of options in these research populations, this means to *strengthen the quality of medical care options* and increase the viable options available.

There has been a discussion as to the medical care duties of clinical trials operating in low-resource settings to the community and a number of guidelines have been produced (Table 1). For example, CIOMS in Guideline 21: *"External sponsors are ethically obliged to ensure the availability of: health-care services that are essential to the safe conduct of the research; treatment for subjects who suffer injury as a consequence of research interventions; and, services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned."*(Council for International Organizations of Medical Sciences & World Health Organization, 2002). The Declaration of Helsinki states in paragraph 9: "*It is the duty of physicians who are involved in medical research to protect the life, health,*

dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.". These guidelines are broad and open to different interpretations - not providing a specific answer around the obligations of the clinical trial itself when this extends beyond the individual participant (Tarantola et al., 2007; World Medical Association, 2013).

CIOMS **(Council for International Organizations of Medical Sciences & World Health Organization, 2002)**	*"External sponsors are ethically obliged to ensure the availability of: health-care services that are essential to the safe conduct of the research; treatment for subjects who suffer injury as a consequence of research interventions; and, services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned."*
Declaration of Helsinki **(World Medical Association, 2013)**	*"It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects."*
Nuffield Council, 2002 **(Nuffield Council on Bioethics, 2002)**	*"The nature of care and treatment that will be provided to participants in research including preventive and curative treatments and diagnostic interventions"* *"When research into preventive measures is conducted, wherever appropriate, participants who develop the disease being studied should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard that should be offered is the best available intervention as part of the national public health system for that disease".*
US National Bioethics Committee: The Charter of the National Bioethics Advisory commission (NBAC) **(National Bioethics Advisory Commission, 2001)**	*"Treatment that is routinely available to the majority of the population of that country"*
2012 publication reporting on a WHO/UNAIDS consultation **(UNAIDS/WHO, 2012)**	*"Participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognised as optimal. Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment".*

Table 1. An overview of the current recommendations on the extent to which vaccine trials should provide medical care.

These guidelines are not step-by-step protocols, instead they are open to interpretation, need to be considered within the target context, and moral reasoning must be applied (Solomon R. Benatar & Singer, 2000).

There are expansive notions of what obligations sponsors have when it comes to strengthening the quality of medical care, with some suggesting they must meet all medical needs (London, 2005; K. Shapiro & Benatar, 2005). In the short-term, providing the gold standard of care for all community members free of charge is likely not economically feasible. However, the supplementation of clinical trial budgets to strengthen local health capacities for the community members will provide alternative options for caregivers and provide a more reasonable choice when deciding to participate in research. What needs to be done to restore caregiver autonomy is to provide care options for all children eligible for the trial that is context-specific. This will generate alternative options and thereby reduce the possibility of inducement related to the free medical care in situations where caregivers have an ill child.

The reduction of regulation around what constitutes medical care under the umbrella of the clinical trial and expanding this into the community will also generate quality medical care options. In HIV vaccine trials, sponsors must outline what medical care they will provide in the research protocol when submitting it for ethical review (UNAIDS/WHO, 2012). I propose that by outlining specifically what medical care will be provided and positioning it relative to the context of the local setting, RECs can determine if there is a need to strengthen the quality of medical care options outside of the trial before and during the research study. This encourages further collaboration with local stakeholders. Engagement with local stakeholders is important to identify the structural needs of a trial site and encourage the responsible stakeholders to contribute to strengthening these medical care options, these stakeholders range from national policy-makers to decision makers at the district level to local community members (Mtove et al., 2018). There is frequently competition between countries for clinical trials and this incentive, combined with national collaboration, can lead to local government commitments to strengthen medical services. Taking this approach and fostering good collaborative research governance can lead to the development of health systems sustainably (Ward et al., 2017; Ward, Shaw, Sprumont, et al., 2018). In the long-term,

strengthening the local health system and thereby improving the quality of medical options available to caregivers, reduces the structural inequities and strengthens caregiver autonomy.

The risk of placing these responsibilities on the sponsor or funder is that demanding such commitments can lead to an overextension of expectations and thereby inhibit research in these settings, especially for neglected tropical diseases, and we cannot stop doing research on these topics. Also providing care may have an inhibitory effect on local governments to invest in health system strengthening in these settings, who do ultimately have the duty of to meet local health needs (Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008). No one actor in the clinical should be responsible for rectifying the structural inequities by providing the highest possible care in a low-resource setting, and while aspirational, we must strive for this care to be accessible for these populations. Therefore, clinical trials must engage in an equitable manner with stakeholders to improve collaborative practice and support local governments in strengthening the quality of local health services (Ward, Shaw, Sprumont, et al., 2018). The level of care provided and to whom will depend on various factors linked to the local contexts and the phase of the clinical trial, but the costs should be shared amongst stakeholders appropriately. This is succinctly put by Kleinman, saying that bioethics should "*be the outcome of reciprocal, participatory engagement across different worlds of experience*" (Kleinman, 1997).

What I hope to convey is the impossibility of an ethical manual providing straight-forward, linear instructions with regards to the establishment of choice or lack-there-of. What needs to be clear is that there are specific duties associated with research in vulnerable populations and the burdens of these duties must be shared amongst actors in a clinical trial. While some of the above recommendations may be aspirational, the urgency with which we need vaccines and therapeutics to target diseases burdening those living in low-resource settings does not justify relaxing ethical standards. The answer is not in banning these trials, as we need to develop tools to tackle diseases endemic to populations in low-resource settings. The answer is also not in removing the free medical care, as the validity of the science requires healthy children and not acting to reduce the number of preventable deaths counteracts the foundational principle of beneficence (preventing

harm). Where we must focus our attention is protecting autonomy and enhancing choice within the boundaries of the clinical trials. It is unfair to the frontline researchers to not the outline medical care obligations of the sponsors in detail and proportional to the local structures available, this leaves them without the means to address the structural inequities (Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008). Leaving front-line researchers ill-equipped to deal with the structural disparities is both inefficient and places an excessive moral weight on the researchers, instead support needs to be provided to frontline researchers where it is needed. To understand these needs and the context of these frontline researchers, I will next explore the researcher experience when working in human communities.

RESEARCHER'S EMBODIED REALITY

While community experiences are often investigated, the personal experience of the researcher is frequently left in the margins. This has generated frameworks outlining the what researchers "owe" their subjects, providing guidance without accounting for the individual story of the researchers (Richardson & Belsky, 2004). This reliance on a single story to paint the whole picture results in skewed interpretations of the contextual reality (Mkhwanazi, 2016). I was in a unique position in this project to gain insight into both the caregiver and the researcher experience in the PMVT.

Moral distress

Through my interviews with the researchers a grappling reality came to light. Local researchers are embedded in these communities during the entire duration of these trials, in the case of the phase III malaria vaccine trial, five years. More so, the researchers are part of an institution that has ongoing research studies in the community and may spend the majority of their careers working with these communities. Being embedded in the community in this way has them balancing the professional commitment to their work and the other roles they inhabit as social human beings. When asking what it is like for the researcher to respond to children seeking treatment who are not enrolled in the trial:

> *"I feel very strange. I feel very funny. I feel cornered. I don't know. But I can never let them go, I will never let them go because I am a parent, I am a grandparent, and I am a researcher. So I feel in all of those perspectives and I appreciate it when the PI allows me to let them be treated."*

This quote reflects the moral dilemma that many researchers working in low-resource settings face, the inequities present and the consequence to human life as a result of the structural disparity.

Earlier, we have established the importance of collaborative partnerships with local stakeholders to reach a consensus about the purview and degree of care to be provided by the clinical trial, particularly in settings with perverse structural inequity. The PMVT case study I investigated in this project provided care to participants beyond the scope of their research question, for instance providing nutritional counselling and emergency care in response to traffic accidents. This has also been the case for other studies in low-resource settings, for example a tuberculosis prevention study in South Africa provided free follow-up HIV care for participants and a vaginal microbicide trial in Benin provided care for the sex worker participants in cases where an extrauterine pregnancy was detected (Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008). Both of those studies were in close partnership with local stakeholders to establish reasonable standards of care with proportionality around both benefits and risks. However, when the scope of ancillary care is not clearly defined or their boundaries prevent the researcher from acting in alignment with their moral norms, an internal conflict is sparked in the researcher on the frontline.

The duty to rescue

Australian philosopher Peter Singer proposed that we have a duty to reduce suffering and death whenever we can (Singer, 1972). This controversial position was further defined as helping those in need when no one else is able to, without significant personal sacrifice, as a universal duty (McIntyre, 1994). Researchers in this project have expressed their internal experience of this duty, in conjunction with the long-term relationship many frontline researchers have with their research participants and communities, as the source of their moral distress in researchers. Particularly when budget constraints hold them back from providing needed care for community members. This led to reports in the study of researchers personally financing medications for family members of participants and grappling with their conflicting obligations to the community and to the research institution. While the duty to rescue is a controversial position, the way researchers experienced the obligations to the community when it is within their own means, was undeniable for them. The long-term relationships these researchers had with community engagement practices and also their

own personal stories as human social beings led to conflicting obligations towards the clinical trial budget constraints and helping those in need.

RELATIONAL ETHICS

The main shortcoming of a principalist ethical approach is that it negates to situate the above realities into the everyday life of the human researcher. Geissler et al. have advocated for a more searching and open frame of ethical rules defined by relational ethics, however they raise the difficulty (and perhaps danger) of abandoning formal principalist ethics and consequently relying on a qausi-legal frame and private morality (P. Wenzel Geissler et al., 2008). Where principal-based ethics provides a solid foundation to guide medical research, relational ethics can complement it by accounting for human decision making in a social context.

Strengthening agency

The introduction frames the questions around the foundational principles. Based on my interviews with both the researchers and participants I have come to better understand the multifaceted nature of clinical trial research in low-resource settings. The research protocol is written to adhere to scientific rigour and generate knowledge, the researchers are implementing it as social beings who make ethical decisions in the context of relationships, and the caregivers are seeking to meet their families' needs. This leaves the researchers in the middle, with an onus of negotiating both their commitments to their protocol and to its subjects. Researchers in our study found ways to negotiate these demands and wherever possible, to meet the medical needs of the children in the study site. Their commitments to members of the community allowed for the establishment of trust, which in turn fostered the sustainability of the relationship between the research institution and the community. Researchers during the interviews spoke about the nicknames that members of the community had coined for them, with one respondent being referred to as "*mother of the site"*, showing the relational hospitality that research teams established beyond the requirements of the foundational principals.

Having this ethics of intimacy and relatedness can complement the foundational principals. As I discussed above, a particularly important aspect of strengthening autonomy is strengthening

the medical care options for the community. Through familial and trusting relationships community members can exchange in a dialogue with researchers to communicate their needs. This fosters the identification of health services that are needed to reduce structural disparities and how they can be strengthened. In turn, these researchers can situate the context in relation to the medical care provided by the trial and identify if there is the possibility of undue inducement as a result of the structural disparity and lack of choice. Relational ethics is necessary to establish the trust of the institution, the researcher and the community and enable a shared-reciprocity to take place.

Trust

Trust plays an important role in clinical trial outcomes (Enria et al., 2016; Kass, Sugarman, Faden, & Schoch-Spana, 1996; Kerasidou, 2017). Through research practices that broke trust, such as the Tuskegee syphilis study, the formal requirements concerning ethical review of research protocols were put into place. When trust is broken in this way it has major implications beyond the scope of the individual research project and into the way those populations respond to future research (Kass et al., 1996). When caregivers consent to enroll their child in clinical trial research there is a degree of implicit trust in the research institution, the regulatory oversight and the researcher.

The most common link between trust and research is with regards to seeking informed consent for research participation (Kerasidou, 2017; V. Marsh, Kamuya, Rowa, Gikonyo, & Molyneux, 2008; Molyneux et al., 2005; Sugarman et al., 1998). The Nuremburg Code established the first guidelines around informed consent in medical research, however the role of informed consent in ethical medical research was recognized as early as the nineteenth century (Vollmann & Winau, 1996). Free and informed consent is often considered the *sine qua non* of good research, however as I discussed earlier, it is also one of the most sensitive and complex parts of clinical research (S. R Benatar, 2002). The researchers I interviewed expressed this link between trust,

transparency and informing participants. They emphasize what is required to maintain trust and the consequences for future research in that setting when it is broken:

> *"What is important in the community is that you must be trusted. They have to trust you. And in research it is good to be trusted and you need to be very straightforward and to the point. Because if you say the truth about a particular study, what procedures will be done, how long do you think they will take per visit, you know around about, and then what blood draws if any. You know and the specifics, then they will trust you and they will do that. But if you tell them one story and do different stories then they will never trust you and they will not continue coming to other studies."*

Frontline researchers reported to be very careful in communicating the details of the procedures and committing to transparent communication, due to the possible implications of broken trust down the road. While aware of this link between transparency and trust, the adept awareness of the relational was also a common string in the interviews. This was heavily situated in the context and the relationship between the researcher, the caregiver and the participant. This extended beyond what researchers "ought" to do as described by their professional code of conduct, for instance the informed consent practices, and into their own sense of the relational context (Participants of an International Workshop in Kenya on the Role of Frontline Staff in Biomedical Research, July 2014 & Kombe, 2015). The link between relational ethics and trust was made explicit in the following narrative told by one of the researcher respondents:

> *"I came in the room, I sat, and I shook her hand and I shook the baby's hand. I even took the baby onto my lap. The baby even leans on me like this, so the mother trusts me with the baby. Then I tell her ok, and I can even sing with your name, I can make a quick song with your name. So she trusts, "she is really good with my baby, this doctor is good with my baby." So when I give her baby back, and now mama so and so we are going to take a sample, remember which visit this is, then she will tell you "oh she forgot" and we will remind her it is visit five. Don't be*

in a hurry. Visit five, how much were we removing? "I forgot. But you know, I was told it was. Oh I was told" then you tell me "visit five we are doing a safety check and we are only removing this. So today we are going to remove this from the baby, we try to get the vein and we hope we shall find the vein once." So just carry the baby like this and position the baby like this like this, then I will give her back her baby. You can even tell her, "eh the baby is smart, eh the baby has a pretty pink dress." You know you praise her, then she believes, oh her heart lowers"

This narrative illustrates relational actions by the researcher and how they can influence the subjective experience of the caregiver. They are not restricted to the dialogic, instead the researcher is embodied in this interpersonal relationship and in attunement with the caregiver and the participant. An emotional engagement with the 'lived life' that fosters a trust based in the understanding of the caregiver and participant as individuals with unique needs (Edwards, 2005). Through being active in the relationships of the moment, the researcher is embedded in a relational context (MacDonald, 2007). Here relational ethics can provide a moral perspective that is supplementary to the foundational principle of beneficence, not merely dialectical, allowing for an engagement with the 'lived life' and providing a deeper ground for the roots of trust to take hold. This trust grows out of reflexive relational embodiment as exhibited in the narrative told by the researcher. The vulnerability of each actor is embraced, and the potential power differential is not extinguished, but acknowledged. This allows for a mutual respect to take hold which opens the door for the researcher to experience the caregiver's reality and discern the context out of which they are making a decision. When researchers are provided with the tools to foster trust and act out of their embodied self, they can strengthen choice and agency in the setting by providing insights into the structural inequities and the ways in which to address them. However, in cases where researchers are not provided the tools this can lead to moral distress. The researcher then becomes enmeshed into the caregiver's reality, experiencing the duty to rescue without the trial resources. Therefore, when asked if a researcher ever personally financed treatment upon a caregiver's request this was the response:

"Yes, I have done that. Yes because sometimes it is terrible. The baby is going to die, because sometimes anemia has set in, HB is like 7, the parasitemia level has actually dropped to five. There is no blood transfusion because the hospitals are on strike. Who will transfuse them? When you get them in to the private hospital they will locked there without bills. So they are there to stay. And the other children are not being taken care of at home and they cannot go to school, they have nothing to eat, so it is all complicated. Because women are the ones who go digging to get money to come and feed the families. Maybe husbands also do small things but are actually not there. So when she is locked in the hospital the other family members are stuck. And they can't eat, they can all be under famine, the five years are the one who is sick, the 4 years, the 3, 2, 1 the one she has. It is complicated. And it happens a lot anyway. The level of poverty, health care. They say healthcare is supposed to be free in this country and it doesn't go like that because systems are not complete. Lab is there, you have to get the lab. Lab will tell you we don't have this reagent go to another facility. Where is the transport? Do you walk with a sick child? They can go to the lab and do all the things and then take drugs in the pharmacy. But they don't have drugs in the pharmacy. Coartem is not in the pharmacy, why? Because the system they have in place for the counties is that they cannot give coartem alone. We give you coartem supply with the rest of the hospital supply and it has not arrived. There is zero in the pharmacy. What happens? It is all complicated and very dangerous for children.

The structural disparity is witnessed and experienced by the embodied researcher, this is a very real reality for the researchers who are relationally deeply involved in the community during long-term trials. The distress of the researchers continues when they arrive home, witnessing their own limitations and the realities of operating in these contexts:

"You keep wondering did I really do it well at the end of the day. Because when you go home and sit and you now analyze how it was in the day, and it is like,

surely did I help that family? Did I help? It haunts you if you did not really do well. It makes you feel bad."

If the researchers were only inhabiting a reality sufficiently accounted for by the principalist approach used to review the study protocol, this moral distress would not exist. However, instead they are unable to meet the demands of their professional duties and their own moral duties. The starkly different reality due to the (medical) structural inadequacy leaves the embodied researcher exposed and vulnerable. While necessary to build trust in this setting, reflexive relational research also calls for the researcher to drop the cloak of indifference (Etherington, 2007). To protect the researcher's vulnerability and honour the participant's and caregiver's realities, the tools to act in settings with structural disparity need to available to frontline researchers. For this we need clearly defined roles and responsibilities corresponding to the actors in the trial from the very beginning of trial design.

Roles and Responsibilities

We have discussed trust and how it can be defined as personal: between the researcher, caregiver and pediatric participant. It can also extend into the regulatory oversight and the institution. As I mentioned earlier, when a caregiver consents to medical research on behalf of a pediatric participant there is an implicit trust in the regulatory oversight. The role of the RECs to protect trust in the research enterprise should therefore always be taken very seriously, Kass et al. outlines, *"those who oversee research should be humbled by the trust patient-subjects have in the research enterprise and should continue to do their best to live up to that trust"* (Kass et al., 1996). Both the RECs and the sponsors detailing the protocols have a responsibility to maintain an ethic of trust, this is done by careful consideration of the protocol. In particular with regards to the contextual structural reality, situating the benefits in relation to the realities inhabited by participants and seeking ways in which to strengthen existing infrastructure when relevant. When it comes to trust and its expansion into the clinical trial, it is helpful to understand the role of each actor in the clinical trial system. This is defined in Table 2.

	Sponsors	Funders	Research Institution	National Health Authorities	Research Ethics Committee	Principal Investigator	Frontline researchers	Communities	Caregivers	Participants
Determine local standard of care	x	x	x	x						
Make a decision on the standard of care in the clinical trial	x	x	x	x	x	x	x	x		
Receive medical care										x
Provide financing for medical care for the whole community				x						
Provide financing for medical care for participants and provide it if a broader scope is necessary	x	x	x	x						
Provide medical care to participants in the trial						x	x			
Strengthen national health system				x						
Review research protocol and supplementary materials					x					
Meet ethical standards in the protocol	x	x	x		x	x	x			
Establish scientific validity	x	x	x	x	x	x	x			
Seek informed consent						x	x			
Collect the data						x	x			
Improve local infrastructure	x	x		x						
Protect the pediatric participant	x		x		x	x	x	x	x	x
Attend scheduled appointments									x	x
Engage the community						x	x			

Table 2. *The roles and responsibilities of actors in a clinical trial in the context of medical services.*

The roles and responsibilities outlined in Table 2 are not exhaustive for all roles associated with clinical trial conduct and are intended to provide guidance, they may vary depending on the context. They are specifically aimed at defining roles pertaining to the challenges around medical services offered and structural inequity in low-resource settings. Through defining the roles of each actor, responsibilities will not be put off until it reaches the frontline researcher, burdening them with unfair duties and generating internal value conflicts. By recognizing the embodied reality of the researcher, supporting them in building trust with the research participants, and sharing the burden of challenges associated with research in low-resources settings the ethical challenges associated with research in low-resource settings can be reduced. This leads to greater agency for the community, caregiver and participant through local structural capacity building.

CONCLUSION

This establishment of the roles that each actor in the clinical trial has can facilitate three key actions in clinical trial design:

1) Recognize the role of the frontline researchers and the tools they need to build trust with caregivers and the community.

2) Identify ways in which to support front line researchers in a way that is appropriate for the context and its structural capacity.

3) Develop collaborative partnerships with local stakeholders to reduce structural inequities and foster sustainable health system strengthening.

These three actions will vary depending on the local context of the clinical trial, making it important to apply them in collaboration with the simple rules outlined in *Communities and clinical trials: A case study from the RTS,S malaria vaccine trials in eastern Africa*. Using complexity theory to work in iteration with the community and caregivers will enable the researcher to hold a relational position that is reflexive to the unique reality of the caregiver and participant. As complexity theory aims to embrace the unpredictability of working in CAS, a relational ethic will complement the principalist foundation by which research ethics is guided.

Project Limitations

This thesis investigated the ethical challenges associated with clinical trial research in low-resource settings. The empirical data was a collection of 78 interviews with caregivers of PMVT participants and 11 interviews with researchers working on a PMVT. There are a number of limitations that stem from the empirical data collection method.

First off, the first language of the caregivers varied depending on the site (Swahili, Dholuo, Lusoga, Luganda, and English). This required me work with research assistants who were fluent in the first language of the respondent and thereby provide me with translations. The research assistants were also not inhabitants of the villages where the interviews were conducted, instead they were coming from Kampala, Kisumu or Dar es Salaam and therefore there were cultural barriers for them as well. The difficulty of working with translations where linguistic and cultural representations are lost, results in the potential to misrepresent responses and limits the applicability of the findings (Squires, 2009). However, through daily field meetings discussing these challenges, inquiring about local slang and reflexivity on behalf of the research assistants and the field team, I believe the impact of translational misrepresentation is minor.

The interviews with the researchers provided unexpected insights into the realities that researchers grapple with. These interviews were limited to the sites in Kenya and not expanded into the PMVT in Uganda and Tanzania. This limits the generalizability of the findings and is only representative of the population investigated. To strengthen the data, an expansion of the study population in the research design would enable a wider scope of applicability for these findings.

This study aimed to capture the ethical challenges in low-resource settings when conducting clinical trials, limiting the generalizability. Through focusing on a malaria vaccine clinical trial and limiting it to East Africa, the corresponding findings are not applicable to all clinical trials in low-resource settings. Furthermore, the interviews with regards to the RTS,S malaria vaccine Phase III clinical trial, were conducted at three sites, with two of those being in Kenya. This resulted in 66% of the data being from the same geographical area and generated a reduced representability of the data for the Tanzanian site.

Finally, the interviews took place between from 3-5 years since the trial had taken place in the communities of the caregivers. This limited respondent recall as many events had taken place

in their life since the trial. This was addressed by formulating questions to promote recall and events that took place during that time and focused on the individual's account of the experience with the clinical trial.

Implications for Future Research

Through the elucidation of factors impacting the choice to participate in research, the realities of frontline researchers and the ways in which responsibilities can be shared across stakeholders in clinical trials this study contributes to the ways in which ethical challenges can be addressed in research design. Future research focusing on the different countries outside of the East African setting investigated here can provide a more expansive interpretation of the findings and strengthen the generalizability. Tied to this, assessing the applicability of the simple rules outlined in this thesis as well as their impact on caregiver choice would contribute greatly to the overall understanding of how to enable research teams to work in iteration during their engagement with the community. Therefore, future research investigating the impact of these rules through both qualitative interviews and quantitative assessments (eg. survey) of the community acceptance of research would be of great benefit.

In large part, this research should not focus on creating new requirements for research teams, instead equip them with the tools necessary to flourish in the existing system and readily adapt to the non-linear nature of conducting clinical trials in human communities.

REFERENCES

Adebamowo, C. A., Mafe, M. A., Yakubu, A. A., Adekeye, J. M., & Jiya, J. Y. (2008). Developing ethical oversight of research in developing countries: Case study of Nigeria. *Ethics for Public Health Research in Africa*, 15.

Agnandji, S. T., Lell, B., Fernandes, J. F., Abossolo, B. P., Methogo, B. G., Kabwende, A. L., … others. (2012). A phase 3 trial of RTS, S/AS01 malaria vaccine in African infants. *The New England Journal of Medicine*, *367*(24), 2284–2295.

Alonso, P. L. (2006). Malaria: deploying a candidate vaccine (RTS,S/AS02A) for an old scourge of humankind. *International Microbiology: The Official Journal of the Spanish Society for Microbiology*, *9*(2), 83–93.

Angwenyi, V., Kamuya, D., Mwachiro, D., Kalama, B., Marsh, V., Njuguna, P., & Molyneux, S. (2014). Complex realities: community engagement for a paediatric randomized controlled malaria vaccine trial in Kilifi, Kenya. *Trials*, *15*, 65. https://doi.org/10.1186/1745-6215-15-65

Ballou, W. R. (2009). The development of the RTS, S malaria vaccine candidate: challenges and lessons. *Parasite Immunology*, *31*(9), 492–500.

Beauchamp, D. E. (1985). Community: the neglected tradition of public health. *The Hastings Center Report*, *15*(6), 28–36.

Beauchamp, T. L., & Childress, J. F. (2009). *Principles of Biomedical Ethics*. Oxford University Press.

Benatar, S. R. (2002). Reflections and recommendations on research ethics in developing countries. *Social Science & Medicine*, *54*(7), 1131–1141. https://doi.org/10.1016/S0277-9536(01)00327-6

Benatar, Solomon R., & Singer, P. A. (2000). A new look at international research ethics. *BMJ*, *321*(7264), 824–826. https://doi.org/10.1136/bmj.321.7264.824

Bhatt, S., Weiss, D. J., Cameron, E., Bisanzio, D., Mappin, B., Dalrymple, U., … Gething, P. W. (2015). The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. *Nature*, *526*(7572), nature15535. https://doi.org/10.1038/nature15535

Braithwaite, J., Churruca, author.), Kat, Ellis, author.), Louise, Long, author.), Janet, Clay-Williams, author.), Roby, Damen, author.), Nikk, … Sciences, H. (2017). *Complexity*

science in healthcare - aspirations, approaches, applications and accomplishments : a white paper. Retrieved from https://trove.nla.gov.au/version/250484668

Byass, P. (2008). Making sense of long-term changes in malaria. *The Lancet*, *372*(9649), 1523–1525. https://doi.org/10.1016/S0140-6736(08)61631-1

Callahan, D. (2003). Individual good and common good: a communitarian approach to bioethics. *Perspectives in Biology and Medicine*, *46*(4), 496–507.

Capra, F., Juarrero, A., Pedro, S., & Uden, J. van. (2009). *Reframing Complexity: Perspectives from the North and South*. Isce Publishing.

Carneiro, I., Roca-Feltrer, A., Griffin, J. T., Smith, L., Tanner, M., Schellenberg, J. A., … Schellenberg, D. (2010). Age-patterns of malaria vary with severity, transmission intensity and seasonality in sub-Saharan Africa: a systematic review and pooled analysis. *PLoS One*, *5*(2), e8988.

Ceesay, S. J., Casals-Pascual, C., Erskine, J., Anya, S. E., Duah, N. O., Fulford, A. J., … Conway, D. J. (2008). Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *The Lancet*, *372*(9649), 1545–1554. https://doi.org/10.1016/S0140-6736(08)61654-2

Chantler, T., Otewa, F., Onyango, P., Okoth, B., Odhiambo, F., Parker, M., & Geissler, P. W. (2013). Ethical Challenges that Arise at the Community Interface of Health Research: Village Reporters' Experiences in Western Kenya. *Developing World Bioethics*, *13*(1), 30–37. https://doi.org/10.1111/dewb.12023

Chuan, V. T., & Schaefer, G. O. (2015, September 23). Research in Resource-Poor Countries. Retrieved November 20, 2018, from The Hastings Center website: https://www.thehastingscenter.org/briefingbook/multinational-research/

Cilliers, P., & Spurrett, D. (1998). Complexity and post-modernism: understanding complex systems. *South African Journal of Philosophy*, *18*(2), 258–274. https://doi.org/10.1080/02580136.1999.10878187

Cohen, J. M., Smith, D. L., Cotter, C., Ward, A., Yamey, G., Sabot, O. J., & Moonen, B. (2012). Malaria resurgence: a systematic review and assessment of its causes. *Malaria Journal*, *11*(1), 1.

Cohen, J., Nussenzweig, V., Vekemans, J., & Leach, A. (2010). From the circumsporozoite protein to the RTS,S/AS candidate vaccine. *Human Vaccines*, *6*(1), 90–96. https://doi.org/10.4161/hv.6.1.9677

Cottingham, M. D., & Fisher, J. A. (2016). Risk and Emotion Among Healthy Volunteers in Clinical Trials. *Social Psychology Quarterly*, *79*(3), 222–242. https://doi.org/10.1177/0190272516657655

Council for International Organizations of Medical Sciences, & World Health Organization (Eds.). (2002). *International ethical guidelines for biomedical research involving human subjects*. Geneva: CIOMS.

Council of Europe. (2007). *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research* (No. Article 15). Retrieved from https://www.coe.int/web/conventions/full-list

Crane, J. (2010). Adverse events and placebo effects: African scientists, HIV, and ethics in the 'global health sciences.' *Social Studies of Science*, *40*(6), 843–870. https://doi.org/10.1177/0306312710371145

Delany, I., Rappuoli, R., & De Gregorio, E. (2014). Vaccines for the 21st century. *EMBO Molecular Medicine*, *6*(6), 708–720. https://doi.org/10.1002/emmm.201403876

Duan, N. (2005). Listening to consumers and HIV vaccine preparedness. *The Lancet*, *365*(9465), 1119–1121. https://doi.org/10.1016/S0140-6736(05)71857-2

Edwards, S. (2005). Toward a Moral Horizon, Nursing Ethics for Leadership and Practice. *Nursing Philosophy*, *6*(2), 156–157. https://doi.org/10.1111/j.1466-769X.2005.00208.x

Eisenberg, L. (1977). The Social Imperatives of Medical Research. *Science*, *198*(4322), 1105–1110. Retrieved from JSTOR.

Emanuel, E. J., Wendler, D., Killen, J., & Grady, C. (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *Journal of Infectious Diseases*, *189*(5), 930–937.

ENDA Graf Sahel. (1993). *La ressource humaine, avenir des terroirs – recherches paysannes au Sénégal*. Paris, France.

Enria, L., Lees, S., Smout, E., Mooney, T., Tengbeh, A. F., Leigh, B., … Larson, H. (2016). Power, fairness and trust: understanding and engaging with vaccine trial participants and

communities in the setting up the EBOVAC-Salone vaccine trial in Sierra Leone. *BMC Public Health*, *16*(1), 1140. https://doi.org/10.1186/s12889-016-3799-x

Essé, C., Utzinger, J., Tschannen, A. B., Raso, G., Pfeiffer, C., Granado, S., … Obrist, B. (2008). Social and cultural aspects of "malaria" and its control in central Côte d'Ivoire. *Malaria Journal*, *7*, 224. https://doi.org/10.1186/1475-2875-7-224

Etherington, K. (2007). Ethical Research in Reflexive Relationships. *Qualitative Inquiry*, *13*(5), 599–616. https://doi.org/10.1177/1077800407301175

Fadare, J. O., Ademowo, O. G., & others. (2010). Ethical issues in malaria vaccine clinical trials: A principle-based approach. *Annals of Tropical Medicine and Public Health*, *3*(1), 35.

Fairhead, J., Leach, M., & Small, M. (2006). Where techno-science meets poverty: medical research and the economy of blood in The Gambia, West Africa. *Social Science & Medicine (1982)*, *63*(4), 1109–1120. https://doi.org/10.1016/j.socscimed.2006.02.018

Farmer, P. (2001). *Infections and Inequalities: The Modern Plagues*. University of California Press.

Farmer, P. (2004a). An Anthropology of Structural Violence. *Current Anthropology*, *45*(3), 305–325. https://doi.org/10.1086/382250

Farmer, P. (2004b). Rethinking Medical Ethics: A View From Below. *Developing World Bioethics*, *4*(1), 17–41.

Fisher, H. R., McKevitt, C., & Boaz, A. (2011). Why do parents enrol their children in research: a narrative synthesis. *Journal of Medical Ethics*, *37*(9), 544–551. https://doi.org/10.1136/jme.2010.040220

Fisher, J. A. (2013). Expanding the frame of "voluntariness" in informed consent: structural coercion and the power of social and economic context. *Kennedy Institute of Ethics Journal*, *23*(4), 355–379.

Fitzgerald, D. W., Marotte, C., Verdier, R. I., Johnson, W. D., & Pape, J. W. (2002). Comprehension during informed consent in a less-developed country. *Lancet (London, England)*, *360*(9342), 1301–1302. https://doi.org/10.1016/S0140-6736(02)11338-9

Galactionova, K., Tediosi, F., Camponovo, F., Smith, T. A., Gething, P. W., & Penny, M. A. (2017). Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa. *Vaccine*, *35*(1), 53–60. https://doi.org/10.1016/j.vaccine.2016.11.042

Gauri, V., & Khaleghian, P. (2002). Immunization in developing countries: Its political and organizational determinants. *World Development*, *30*(12), 2109–2132. https://doi.org/10.1016/S0305-750X(02)00151-1

Geissler, P. W., & Pool, R. (2006). Editorial: Popular concerns about medical research projects in sub-Saharan Africa--a critical voice in debates about medical research ethics. *Tropical Medicine & International Health: TM & IH*, *11*(7), 975–982. https://doi.org/10.1111/j.1365-3156.2006.01682.x

Geissler, P. Wenzel. (2005). 'Kachinja are Coming!': Encounters Around Medical Research Work in a Kenyan Village. *Africa*, *75*(2), 173–202. https://doi.org/10.3366/afr.2005.75.2.173

Geissler, P. Wenzel, Kelly, A., Imoukhuede, B., & Pool, R. (2008). 'He is now like a brother, I can even give him some blood'--relational ethics and material exchanges in a malaria vaccine "trial community" in The Gambia. *Social Science & Medicine (1982)*, *67*(5), 696–707. https://doi.org/10.1016/j.socscimed.2008.02.004

Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries. (2008). The Ancillary-Care Obligations of Medical Researchers Working in Developing Countries. *PLoS Medicine*, *5*(5). https://doi.org/10.1371/journal.pmed.0050090

Gikonyo, C., Bejon, P., Marsh, V., & Molyneux, S. (2008). Taking social relationships seriously: Lessons learned from the informed consent practices of a vaccine trial on the Kenyan Coast. *Social Science & Medicine (1982)*, *67*(5), 708–720. https://doi.org/10.1016/j.socscimed.2008.02.003

Gikonyo, C., Kamuya, D., Mbete, B., Njuguna, P., Olotu, A., Bejon, P., … Molyneux, S. (2013). Feedback of research findings for vaccine trials: experiences from two malaria vaccine trials involving healthy children on the Kenyan Coast. *Developing World Bioethics*, *13*(1), 48–56. https://doi.org/10.1111/dewb.12010

Gilchrist, A. (2000). The well-connected community: networking to the edge of chaos. *Community Development Journal*, *35*(3), 264–275.

Glantz, L. H., Annas, G. J., Grodin, M. A., & Mariner, W. K. (1998). Research in developing countries: taking "benefit" seriously. *The Hastings Center Report*, *28*(6), 38–42.

Glickman, S. W., McHutchison, J. G., Peterson, E. D., Cairns, C. B., Harrington, R. A., Califf, R. M., & Schulman, K. A. (2009). Ethical and Scientific Implications of the Globalization of Clinical Research. *New England Journal of Medicine*, *360*(8), 816–823. https://doi.org/10.1056/NEJMsb0803929

Global Forum for Health Research Organization. (2004). *10/90 Report on Health Research 2003-2004*. Geneva, Switzerland: Global Forum for Health Research.

Gomersall, T. (2018). Complex adaptive systems: a new approach for understanding health practices. *Health Psychology Review*, *12*(4), 405–418. https://doi.org/10.1080/17437199.2018.1488603

Graboyes, M. (2015). *The experiment must continue: medical research and ethics in East Africa, 1940-2014*. Athens: Ohio University Press.

Gulland, A. (2015). Malaria vaccine difficult to roll out because four doses are needed, WHO says. *BMJ*, *351*, h5706. https://doi.org/10.1136/bmj.h5706

Hahn, R. A., & Inhorn, M. C. (1999). *Anthropology and Public Health: Bridging Differences in Culture and Society*. Oxford University Press.

Haire, B. G., & Ogundokun, O. (2014). *Ethics of Ancillary Care in Clinical Trials in Low Income Countries: A Nigerian Case Study*. 8.

Hamel, M., Oneko, M., Williamson, J., Sewe, M., Kariuki, S., Odhiambo, F., … Laserson, K. F. (2014). *A marked reduction in mortality among participants in a clinical trial that removed barriers to care and implemented national case management guidelines*.

Hayden, C. (2007). Taking as Giving: Bioscience, Exchange, and the Politics of Benefit-Sharing. *Social Studies of Science*, *37*(5), 729–758.

Helbing, D. (2013). Globally networked risks and how to respond. *Nature*, *497*(7447), 51–59. https://doi.org/10.1038/nature12047

Helman, C. G. (2007). *Culture, Health and Illness, Fifth edition*. CRC Press.

Hendrix, K. S., Sturm, L. A., Zimet, G. D., & Meslin, E. M. (2016). Ethics and childhood vaccination policy in the United States. *American Journal of Public Health*, *106*(2), 273–278.

Holland, J. H. (2014). *Complexity: A Very Short Introduction*. Oxford, New York: Oxford University Press.

IJsselmuiden, C. B., & Faden, R. R. (1992). Research and informed consent in Africa--another look. *The New England Journal of Medicine*, *326*(12), 830–833. https://doi.org/10.1056/NEJM199203193261212

Jagosh, J., Macaulay, A. C., Pluye, P., Salsberg, J., Bush, P. L., Henderson, J., … Greenhalgh, T. (2012). Uncovering the benefits of participatory research: implications of a realist review for health research and practice. *The Milbank Quarterly*, *90*(2), 311–346. https://doi.org/10.1111/j.1468-0009.2012.00665.x

Jamrozik, E., Fuente-Núñez, V., Reis, A., Ringwald, P., & Selgelid, M. J. (2015). Ethical aspects of malaria control and research. *Malaria Journal*, *14*(1), 1.

Johnson, D. A., Joosten, Y. A., Wilkins, C. H., & Shibao, C. A. (2015). Case Study: Community Engagement and Clinical Trial Success: Outreach to African American Women. *Clinical and Translational Science*, *8*(4), 388–390. https://doi.org/10.1111/cts.12264

Kass, N. E., Sugarman, J., Faden, R., & Schoch-Spana, M. (1996). Trust, The fragile foundation of contemporary biomedical research. *The Hastings Center Report*, *26*(5), 25–29.

Kenny, N. P., Sherwin, S. B., & Baylis, F. E. (2010). Re-visioning public health ethics: a relational perspective. *Canadian Journal of Public Health/Revue Canadienne de Sante'e Publique*, 9–11.

Kerasidou, A. (2017). Trust me, I'm a researcher!: The role of trust in biomedical research. *Medicine, Health Care, and Philosophy*, *20*(1), 43–50. https://doi.org/10.1007/s11019-016-9721-6

Khan, S., Vandermorris, A., Shepherd, J., Begun, J. W., Lanham, H. J., Uhl-Bien, M., & Berta, W. (2018). Embracing uncertainty, managing complexity: applying complexity thinking principles to transformation efforts in healthcare systems. *BMC Health Services Research*, *18*. https://doi.org/10.1186/s12913-018-2994-0

Kingori, P. (2015). The "empty choice": A sociological examination of choosing medical research participation in resource-limited Sub-Saharan Africa. *Current Sociology. La Sociologie Contemporaine*, *63*(5), 763–778. https://doi.org/10.1177/0011392115590093

Kingori, P., Muchimba, M., Sikateyo, B., Amadi, B., & Kelly, P. (2010). "Rumours" and clinical trials: a retrospective examination of a paediatric malnutrition study in Zambia, southern Africa. *BMC Public Health*, *10*(1), 556. https://doi.org/10.1186/1471-2458-10-556

Kithinji, C., & Kass, N. E. (2010). Assessing the Readability of Non-English-Language Consent Forms: The Case of Kiswahili for Research Conducted in Kenya. *IRB*, *32*(4), 10–15.

Klein, S. L., Shann, F., Moss, W. J., Benn, C. S., & Aaby, P. (2016). RTS,S Malaria Vaccine and Increased Mortality in Girls. *MBio*, *7*(2), e00514-16. https://doi.org/10.1128/mBio.00514-16

Kleinman, A. (1997). *Writing at the Margin: Discourse Between Anthropology and Medicine*. University of California Press.

Kruger, M., Ndebele, P., & Horn, L. (2014). *Research ethics in Africa: a resource for research ethics committees*.

Kulkarni, P. S. (2013). Current topics in research ethics in vaccine studies. *Perspectives in Clinical Research*, *4*(1), 80.

Langlois, A. (2008). The UNESCO Universal Declaration on Bioethics and Human Rights: perspectives from Kenya and South Africa. *Health Care Analysis: HCA: Journal of Health Philosophy and Policy*, *16*(1), 39–51. https://doi.org/10.1007/s10728-007-0055-7

Lantz, P. M., Israel, B., Schulz, A. J., & Reyes, A. G. (2017). Community-based participatory research: rationale and relevance for social epidemiology. In *179–211*. *Methods in social epidemiology, Second edition*. Jossey-Bass & Pfeiffer Imprint Wiley.

Launiala, A., & Kulmala, T. (2006). The importance of understanding the local context: women's perceptions and knowledge concerning malaria in pregnancy in rural Malawi. *Acta Tropica*, *98*(2), 111–117. https://doi.org/10.1016/j.actatropica.2005.12.008

Lavery, J. V. (2018). 'Wicked problems', community engagement and the need for an implementation science for research ethics. *Journal of Medical Ethics*, *44*(3), 163–164. https://doi.org/10.1136/medethics-2016-103573

Loff, B., Jenkins, C., Ditmore, M., Overs, C., & Barbero, R. (2005). Unethical clinical trials in Thailand: a community response. *The Lancet*, *365*(9471), 1618–1619. https://doi.org/10.1016/S0140-6736(05)66502-6

London, A. J. (2005). Justice and the Human Development Approach to International Research. *Hastings Center Report*, *35*(1), 24–37. https://doi.org/10.1353/hcr.2005.0009

Luhmann, N. (1995). *Social Systems*. Stanford University Press.

MacDonald, H. (2007). Relational ethics and advocacy in nursing: literature review. *Journal of Advanced Nursing*, *57*(2), 119–126. https://doi.org/10.1111/j.1365-2648.2006.04063.x

Macklin, R. (2003). Bioethics, Vulnerability, and Protection. *Bioethics*, *17*(5–6), 472–486. https://doi.org/10.1111/1467-8519.00362

Maguire, S., McKelvey, B., Mirabeau, L., & Oztas, N. (2006). Complexity Science and Organization Studies. In *The SAGE Handbook of Organization Studies* (2nd ed., pp. 165–214). https://doi.org/10.4135/9781848608030

Malaria Vaccine Funders Group. (2013). Malaria Vaccine Technology Roadmap. Retrieved September 9, 2016, from http://www.who.int/immunization/topics/malaria/vaccine_roadmap/TRM_update_nov13.pdf?ua=1

Marsh, V., Kamuya, D., Rowa, Y., Gikonyo, C., & Molyneux, S. (2008). Beginning community engagement at a busy biomedical research programme: Experiences from the KEMRI CGMRC-Wellcome Trust Research Programme, Kilifi, Kenya. *Social Science & Medicine*, *67*(5), 721–733. https://doi.org/10.1016/j.socscimed.2008.02.007

Marsh, V. M., Kamuya, D. K., Parker, M. J., & Molyneux, C. S. (2011). Working with Concepts: The Role of Community in International Collaborative Biomedical Research. *Public Health Ethics*, *4*(1), 26–39. https://doi.org/10.1093/phe/phr007

Mathews, K. M., White, M. C., & Long, R. G. (1999). Why Study the Complexity Sciences in the Social Sciences? *Human Relations*, *52*(4), 439–462. https://doi.org/10.1177/001872679905200402

McDaniel, R. R., Driebe, D. J., & Lanham, H. J. (2013). Health care organizations as complex systems: new perspectives on design and management. *Advances in Health Care Management*, *15*, 3–26.

McIntyre, A. (1994). Guilty Bystanders? On the Legitimacy of Duty to Rescue Statutes. *Philosophy & Public Affairs*, *23*(2), 157–191. Retrieved from JSTOR.

Merritt, M. W., Taylor, H. A., & Mullany, L. C. (2010). Ancillary Care in Community-Based Public Health Intervention Research. *American Journal of Public Health*, *100*(2), 211–216. https://doi.org/10.2105/AJPH.2009.168393

Mill, J. S. (1859). *On Liberty*. Retrieved from https://www.bartleby.com/130/

Miller, L., Folayan, M., Allman, D., Nkala, B., Kasirye, L. M., Mingote, L. R., … Ditmore, M. (2010). How ethical is your clinical trial? *International Journal of Clinical Practice*, *64*(9), 1179–1182. https://doi.org/10.1111/j.1742-1241.2010.02421.x

Mitchell, K., Nakamanya, S., Kamali, A., & Whitworth, J. A. G. (2002). Balancing rigour and acceptability: the use of HIV incidence to evaluate a community-based randomised trial in rural Uganda. *Social Science & Medicine*, *54*(7), 1081–1091. https://doi.org/10.1016/S0277-9536(01)00082-X

Mkhwanazi, N. (2016). Medical Anthropology in Africa: The Trouble with a Single Story. *Medical Anthropology*, *35*(2), 193–202. https://doi.org/10.1080/01459740.2015.1100612

Molyneux, C. S., Peshu, N., & Marsh, K. (2004). Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast. *Social Science & Medicine (1982)*, *59*(12), 2547–2559. https://doi.org/10.1016/j.socscimed.2004.03.037

Molyneux, C. S., Peshu, N., & Marsh, K. (2005). Trust and informed consent: insights from community members on the Kenyan coast. *Social Science & Medicine (1982)*, *61*(7), 1463–1473. https://doi.org/10.1016/j.socscimed.2004.11.073

Montgomery, C. M., & Pool, R. (2017). From 'trial community' to 'experimental publics': how clinical research shapes public participation. *Critical Public Health*, *27*(1), 50–62. https://doi.org/10.1080/09581596.2016.1212161

Mtenga, S., Kimweri, A., Romore, I., Ali, A., Exavery, A., Sicuri, E., … Kafuruki, S. (2016). Stakeholders' opinions and questions regarding the anticipated malaria vaccine in Tanzania. *Malaria Journal*, *15*, 189. https://doi.org/10.1186/s12936-016-1209-6

Mtove, G., Kimani, J., Kisinza, W., Makenga, G., Mangesho, P., Duparc, S., … Vandenbroucke, P. (2018). Multiple-level stakeholder engagement in malaria clinical trials: addressing the challenges of conducting clinical research in resource-limited settings. *Trials*, *19*(1), 190. https://doi.org/10.1186/s13063-018-2563-1

Mwenesi, H. A. (2005). Social science research in malaria prevention, management and control in the last two decades: an overview. *Acta Tropica*, *95*(3), 292–297. https://doi.org/10.1016/j.actatropica.2005.06.004

National Bioethics Advisory Commission. (2001). *Ethical and policy issues in international research: clinical trials in developing countries.* Bethesda, Md: National Bioethics Advisory Commission.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report* [Text]. Retrieved from Department of Health,

Education and Welfare website: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Neely, K. (2015). Complex adaptive systems as a valid framework for understanding community level development. *Development in Practice*, *25*(6), 785–797. https://doi.org/10.1080/09614524.2015.1060949

Nichter, M. (1995). Vaccinations in the third world: A consideration of community demand. *Social Science and Medicine*, *41*(5), 617–632. https://doi.org/10.1016/0277-9536(95)00034-5

Nigeria Ministry of Health. (2007). National Code for Health Research Ethics of the Federal Republic of Nigeria. Retrieved September 9, 2016, from http://www.nhrec.net/nhrec/NCHRE_Aug%2007.pdf

Nuffield Council on Bioethics. (2002). The ethics of research related to healthcare in developing countries. Retrieved November 13, 2018, from Nuffield Bioethics website: http://nuffieldbioethics.org/project/research-developing-countries

Nyika, A., Chilengi, R., Ishengoma, D., Mtenga, S., Thera, M. A., Sissoko, M. S., … Kilama, W. L. (2010). Engaging diverse communities participating in clinical trials: case examples from across Africa. *Malaria Journal*, *9*, 86. https://doi.org/10.1186/1475-2875-9-86

Obrist, B., Iteba, N., Lengeler, C., Makemba, A., Mshana, C., Nathan, R., … Mshinda, H. (2007). Access to Health Care in Contexts of Livelihood Insecurity: A Framework for Analysis and Action. *PLOS Medicine*, *4*(10), e308. https://doi.org/10.1371/journal.pmed.0040308

Ojakaa, D. I., Ofware, P., Machira, Y. W., Yamo, E., Collymore, Y., Ba-Nguz, A., … Bingham, A. (2011). Community perceptions of malaria and vaccines in the South Coast and Busia regions of Kenya. *Malaria Journal*, *10*. https://doi.org/10.1186/1475-2875-10-147

O'Meara, W. P., Bejon, P., Mwangi, T. W., Okiro, E. A., Peshu, N., Snow, R. W., … Marsh, K. (2008). Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *The Lancet*, *372*(9649), 1555–1562. https://doi.org/10.1016/S0140-6736(08)61655-4

Paré Toe, L., Ravinetto, R. M., Dierickx, S., Gryseels, C., Tinto, H., Rouamba, N., … Peeters Grietens, K. (2013). Could the decision of trial participation precede the informed consent process? Evidence from Burkina Faso. *PloS One*, *8*(11), e80800. https://doi.org/10.1371/journal.pone.0080800

Participants of an International Workshop in Kenya on the Role of Frontline Staff in Biomedical Research, July 2014, & Kombe, F. (2015). Enhancing quality and integrity in biomedical research in Africa: an international call for greater focus, investment and standardisation in capacity strengthening for frontline staff. *BMC Medical Ethics*, *16*(1), 77. https://doi.org/10.1186/s12910-015-0071-3

Penny, M. A., Verity, R., Bever, C. A., Sauboin, C., Galactionova, K., Flasche, S., … Ghani, A. C. (2016). Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *The Lancet*, *387*(10016), 367–375. https://doi.org/10.1016/S0140-6736(15)00725-4

Pollard, C. L. (2015). *What is the Right Thing to Do: Use of a Relational Ethic Framework to Guide Clinical Decision-Making*. 7.

Pratt, B., & de Vries, J. (2018). Community engagement in global health research that advances health equity. *Bioethics*, *32*(7), 454–463. https://doi.org/10.1111/bioe.12465

Ramalingam, B., Jones, H., & Overseas Development Institute (London, E. (2008). *Exploring the science of complexity: ideas and implications for development and humanitarian efforts*. London: Overseas Development Institute.

Rhodes, S. D., Malow, R. M., & Jolly, C. (2010). Community-based participatory research (CBPR): A new and not-so-new approach to HIV/AIDS prevention, care, and treatment. *AIDS Education and Prevention*, *22*(3), 173–183. https://doi.org/10.1521/aeap.2010.22.3.173

Richardson, H. S., & Belsky, L. (2004). The ancillary-care responsibilities of medical researchers. An ethical framework for thinking about the clinical care that researchers owe their subjects. *The Hastings Center Report*, *34*(1), 25–33.

Roll Back Malaria Partnership/World Health Organization. (2008). *Global Malaria Action Plan 1 (2000–2015) (World Health Organization, 2008)*.

Romore, I., Ali, A. M., Semali, I., Mshinda, H., Tanner, M., & Abdulla, S. (2015). Assessment of parental perception of malaria vaccine in Tanzania. *Malaria Journal*, *14*, 355. https://doi.org/10.1186/s12936-015-0889-7

Rowe, A. K., Steketee, R. W., Arnold, F., Wardlaw, T., Basu, S., Bakyaita, N., … others. (2007). Viewpoint: Evaluating the impact of malaria control efforts on mortality in sub-Saharan Africa. *Tropical Medicine & International Health*, *12*(12), 1524–1539.

RTS,S Clinical Trials Partnership. (2015a). Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet (London, England)*, *386*(9988), 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8

RTS,S Clinical Trials Partnership. (2015b). Study Protocol: Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet (London, England)*, *386*(9988), 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8

Sauboin, C. J., Bellinghen, L.-A., Velde, N., & Vlaenderen, I. (2015). Potential public health impact of RTS, S malaria candidate vaccine in sub-Saharan Africa: a modelling study. *Malaria Journal*, *14*(1), 1.

Sawyer, R. K. (2003). Artificial Societies: Multiagent Systems and the Micro-Macro Link in Sociological Theory. *Sociological Methods & Research*, *31*(3), 325–363. https://doi.org/10.1177/0049124102239079

Sawyer, R. K. (2005). *Social Emergence: Societies As Complex Systems*. Cambridge University Press.

Schaetti, C., Chaignat, C.-L., Hutubessy, R., Khatib, A. M., Ali, S. M., Schindler, C., & Weiss, M. G. (2011). Social and cultural determinants of anticipated acceptance of an oral cholera vaccine prior to a mass vaccination campaign in Zanzibar. *Human Vaccines*, *7*(12), 1299–1308. https://doi.org/10.4161/hv.7.12.18012

Shapiro, H. T., & Meslin, E. M. (2001). Ethical issues in the design and conduct of clinical trials in developing countries. *The New England Journal of Medicine*, *345*(2), 139–142. https://doi.org/10.1056/NEJM200107123450212

Shapiro, K., & Benatar, S. R. (2005). HIV prevention research and global inequality: steps towards improved standards of care. *Journal of Medical Ethics*, *31*(1), 39–47. https://doi.org/10.1136/jme.2004.008102

Sherwin, S. (1992). *No Longer Patient: Feminist Ethics and Health Care*. Temple University Press.

Shubis, K., Juma, O., Sharifu, R., Burgess, B., & Abdulla, S. (2009). Challenges of establishing a Community Advisory Board (CAB) in a low-income, low-resource setting: experiences

from Bagamoyo, Tanzania. *Health Research Policy and Systems*, *7*, 16. https://doi.org/10.1186/1478-4505-7-16

Simple Rules. (n.d.). Retrieved January 25, 2019, from Human Systems Dynamics Institute website: https://www.hsdinstitute.org/resources/simple-rules.html

Singer, P. (1972). Famine, Affluence, and Morality. *Philosophy and Public Affairs*, *1*(3), 229–243.

Sirima, S. B., Mordmüller, B., Milligan, P., Ngoa, U. A., Kironde, F., Atuguba, F., … GMZ2 Trial Study Group. (2016). A phase 2b randomized, controlled trial of the efficacy of the GMZ2 malaria vaccine in African children. *Vaccine*, *34*(38), 4536–4542. https://doi.org/10.1016/j.vaccine.2016.07.041

Snow, R. W., Omumbo, J. A., Lowe, B., Molyneux, C. S., Obiero, J.-O., Palmer, A., … Marsh, K. (1997). Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *The Lancet*, *349*(9066), 1650–1654. https://doi.org/10.1016/S0140-6736(97)02038-2

Squires, A. (2009). Methodological challenges in cross-language qualitative research: A research review. *International Journal of Nursing Studies*, *46*(2), 277–287. https://doi.org/10.1016/j.ijnurstu.2008.08.006

Stanton, B. F. (2004). *Assessment of Relevant Cultural Considerations is Essential for the Success of a Vaccine*. 7.

Strauss, A., & Corbin, J. (1998). *Basics of qualitative research: Techniques and procedures for developing grounded theory* . Retrieved from http://psycnet.apa.org/psycinfo/1999-02001-000

Streefland, P. H. (2003a). Introduction of a HIV vaccine in developing countries: social and cultural dimensions. *Vaccine*, *21*(13), 1304–1309. https://doi.org/10.1016/S0264-410X(02)00685-0

Streefland, P. H. (2003b). Introduction of a HIV vaccine in developing countries: social and cultural dimensions. *Vaccine*, *21*(13–14), 1304–1309.

Sugarman, J., Kass, N. E., Goodman, S. N., Perentesis, P., Fernandes, P., & Faden, R. R. (1998). What patients say about medical research. *IRB*, *20*(4), 1–7.

Tarantola, D., Macklin, R., Reed, Z. H., Kieny, M. P., Osmanov, S., Stobie, M., & Hankins, C. (2007). Ethical considerations related to the provision of care and treatment in vaccine trials. *Vaccine*, *25*(26), 4863–4874. https://doi.org/10.1016/j.vaccine.2007.03.022

Tindana, P. O., Singh, J. A., Tracy, C. S., Upshur, R. E. G., Daar, A. S., Singer, P. A., … Lavery, J. V. (2007). Grand challenges in global health: community engagement in research in developing countries. *PLoS Medicine*, *4*(9), e273. https://doi.org/10.1371/journal.pmed.0040273

UNAIDS/WHO. (2012). Ethical considerations in biomedical HIV prevention trials. Retrieved March 29, 2019, from http://www.unaids.org/en/resources/documents/2012/20120701_jc1399_ethical_considerations

Vallely, A., Shagi, C., Kasindi, S., Desmond, N., Lees, S., Chiduo, B., … the Microbicides Development Programme. (2007). The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health*, *7*(1), 133. https://doi.org/10.1186/1471-2458-7-133

van den Berg, M., Ogutu, B., Sewankambo, N., Merten, S., Biller-Andorno, N., & Tanner, M. (2019a). Clinical trials in low-resource settings: the perspectives of caregivers of paediatric participants from Uganda, Tanzania and Kenya. *Vaccine (Submitted)*.

van den Berg, M., Ogutu, B., Sewankambo, N., Merten, S., Biller-Andorno, N., & Tanner, M. (2019b). RTS,S malaria vaccine pilot studies: addressing the human realities in large-scale clinical trials. *Vaccine (Submitted)*.

van den Berg, Machteld, Ogutu, Bernhards, Sewankambo, Nelson, Merten, Sonja, Biller-Andorno, Nikola, & Tanner, Marcel. (2019). *Applying complexity theory to model the operation of clinical trials in human communities*.

Vischer, N., Pfeiffer, C., Limacher, M., & Burri, C. (2017). “You can save time if…”-A qualitative study on internal factors slowing down clinical trials in Sub-Saharan Africa. *PloS One*, *12*(3), e0173796. https://doi.org/10.1371/journal.pone.0173796

Vollmann, J., & Winau, R. (1996). Informed consent in human experimentation before the Nuremberg code. *BMJ*, *313*(7070), 1445–1447. https://doi.org/10.1136/bmj.313.7070.1445

Walker, R. L., Cottingham, M. D., & Fisher, J. A. (2018). Serial Participation and the Ethics of Phase 1 Healthy Volunteer Research. *The Journal of Medicine and Philosophy*, *43*(1), 83–114. https://doi.org/10.1093/jmp/jhx033

Ward, C. L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., & Elger, B. (2017). Defining Health Research for Development: The perspective of stakeholders from an international health research partnership in Ghana and Tanzania. *Developing World Bioethics*. https://doi.org/10.1111/dewb.12144

Ward, C. L., Shaw, D., Anane-Sarpong, E., Sankoh, O., Tanner, M., & Elger, B. (2018). The ethics of health care delivery in a pediatric malaria vaccine trial: The perspectives of stakeholders from Ghana and Tanzania. *Journal of Empirical Research on Human Research Ethics*, *13*(1), 26–41.

Ward, C. L., Shaw, D., Sprumont, D., Sankoh, O., Tanner, M., & Elger, B. (2018). Good collaborative practice: reforming capacity building governance of international health research partnerships. *Globalization and Health*, *14*(1), 1. https://doi.org/10.1186/s12992-017-0319-4

Weijer, C., & Emanuel, E. J. (2000). Ethics. Protecting communities in biomedical research. *Science (New York, N.Y.)*, *289*(5482), 1142–1144.

Wendler, D., & Shah, S. (2015). Involving Communities in Deciding What Benefits They Receive in Multinational Research. *The Journal of Medicine and Philosophy*, *40*(5), 584–600. https://doi.org/10.1093/jmp/jhv017

WHO. (2016). Malaria vaccine: WHO position paper, January 2016 – Recommendations. *Vaccine*. https://doi.org/10.1016/j.vaccine.2016.10.047

WHO. (2017a). Clinical evaluation of vaccines. Retrieved December 12, 2018, from WHO website: http://www.who.int/biologicals/vaccines/clinical_evaluation/en/

WHO. (2017b). WHO | Pilot implementation of first malaria vaccine recommended by WHO advisory groups. Retrieved September 10, 2016, from http://www.who.int/mediacentre/news/releases/2015/sage/en/

WHO. (2017c). WHO | Tables of malaria vaccine projects globally. Retrieved December 18, 2018, from WHO website: http://www.who.int/immunization/research/development/Rainbow_tables/en/

WHO. (2018a). WHO | Q&A on the malaria vaccine implementation programme (MVIP). Retrieved November 5, 2018, from WHO website: http://www.who.int/malaria/media/malaria-vaccine-implementation-qa/en/

WHO. (2018b). World Malaria Report. Retrieved March 13, 2019, from WHO website: http://www.who.int/malaria/publications/world-malaria-report-2018/en/

WHO. (2019). WHO vaccine pipeline tracker. Retrieved November 11, 2017, from WHO website: http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/

Williams, H. A. H. A., & Jones, C. O. H. (2004). A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made? *Social Science & Medicine (1982)*, *59*(3), 501–523. https://doi.org/10.1016/j.socscimed.2003.11.010

World Health Organization, World Health Organization, & Global Malaria Programme. (2015). *Global technical strategy for malaria, 2016-2030*.

World Medical Association. (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA*, *310*(20), 2191–2194. https://doi.org/10.1001/jama.2013.281053

Zimet, G. D., Liddon, N., Rosenthal, S. L., Lazcano-Ponce, E., & Allen, B. (2006). Chapter 24: Psychosocial aspects of vaccine acceptability. *Vaccine*, *24*, S201–S209. https://doi.org/10.1016/j.vaccine.2006.06.017

APPENDICES

Index

1. Informed Consent form Caregivers
2. Semi-structured interview guide caregivers
3. Informed Consent form Researchers
4. Semi-structured interview guide researchers
5. CV Machteld van den Berg

Ethical Implications of the Malaria Vaccine Development

Informed consent form caregivers

Part I: Information Sheet

Introduction

I am Machteld van den Berg, a student at the Swiss Tropical and Public Health Institute. I am doing research that relates to ethical implications on malaria vaccine. I am going to give you information which will enable you make decision on whether to participate in this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

This consent form may contain words that you do not understand. Please ask me or stop as we go through the information and I will take time to explain. If you have questions later, you can ask them.

Purpose of the research

Malaria is a very common disease in this country and in sub-Saharan Africa which makes many people particularly children sick. Despite existing strategies to combat malaria in your community, we would

like to make further improvement and discourage disease transmission and associated deaths. We believe that you can help us doing this by telling us what you know both about malaria and about a vaccine that was tested against it. We want to learn what people who live here know about the causes of malaria and the things you do to stop yourself and your children from getting malaria. We want to know these things because this knowledge might help us to learn how we can better control malaria in your community.

Participant Selection

You are being invited to take part in this research because we think that your experience as a mother can contribute much to our understanding and knowledge of local health practices and beliefs.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. The choice that you make will have no bearing on your job or on any work-related evaluations or reports. You may change your mind later and stop participating even if you agreed earlier.

Research procedures

A. We are asking you to participate in research. If you accept, you will be asked to indicate your consent in the informed consent form. Thereafter you will take part in an interview with us which will take about one hour.

B. Interviews with myself and a local translator.

During the interview, we will sit down with you in a comfortable privacy place. If it is better for you, the interview can take place in your home or a friend's home. You will be requested to answer a series of questions during the interview. The interviewer will move from one question to the next question. There will be no wrong response. Every response will be valued. No one else but the interviewer will be present. The information recorded is confidential, and no one else except the project leader and research assistant will access the information documented during your

interview. The entire interview will be tape-recorded based on your consent, but no-one will be identified by name on the tape. The tape will be kept secured in the office. The information recorded is confidential, and no one else except the research assistant and myself will have access to the tapes. The tapes will be destroyed after 1 year.

Duration

We will conduct one interview and the interview will take about 1 hour.

Risks

There is a risk that you may share some personal or confidential information by chance, or that you may feel uncomfortable talking about some of the topics. However, we will ensure an intense confidential of information that you provide. You do not have to answer any question or take part in the interview if you feel the question(s) are too personal or if talking about them makes you uncomfortable. We will also try as much as possible not to make the interview long unnecessary.

Benefits

There will be no direct benefit to you, but your participation is likely to help us find out more about how to improve malaria prevention strategies in your community.

Reimbursements

There will be a payment of 200 Kenyan Shillings as compensation for your time.

Confidentiality of Information

The research being done in the community may draw attention and if you participate you may be asked questions by other people in the community. We will not be sharing information about you to anyone outside of the research team. The information that we collect from this research project will be kept

private. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

Nothing that you tell us today will be shared with anybody outside the research team, and nothing will be attributed to you by name. The knowledge that we get from this research will be shared with you and your community before it is made widely available to the public. Following the meetings, we will publish the results so that other interested people may learn from the research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so, and choosing to participate will not affect your access child's access to vaccination in the future. You may stop participating in the interview at any time that you wish. I will give you an opportunity at the end of the interview to review your remarks, and you can ask to modify or remove portions of those, if you do not agree with my notes or if I did not understand you correctly.

Who to Contact

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact any of the following: Ms. Florence Were fachieng@kemricdc.org number 720 251 082; Machteld van den Berg, machteld.vandenberg@uzh.ch, +41 077 414 0594. If you have questions that relates to ethical issues you may contact the IHI-IRB administrator:

Part II: Certificate of Consent

I have been invited to participate in research about malaria and my child's experience with vaccination.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate [1]

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

[1] A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

- A one hour interview discussing malaria perception and vaccination experience

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Caregiver interview guide

INTRODUCTION

My name is Machteld van den Berg and I am a student from Switzerland studying malaria. I am interested in learning more about your experience with malaria and the vaccine.

Is it alright for you if I record the interview? No one except myself, the research assistant will have access to the recording and if you decide that you would like me to delete the recording, I will do this.

Is it alright for you to start the interview?

MALARIA

1. What do you understand about malaria disease? What is the sickness?

   Prompt: Can you describe the disease to me?

   How do people behave? How do people get healthy again?

   Is it the same with children?

2. What sorts of things should you do so you do not get malaria?

3. What do you do if someone has a fever? How do you know if it is Malaria?

   Probe: can the clinic here help?

4. What is hard about accessing care?

VACCINES

5. Where do the people take their children to get their vaccinations?

   Probe: does this stop them from getting sick?

   What do you think this does?

6. What was the condition of the child after receiving the malaria vaccine?

   Prompt: Can you describe the changes?

7. What is the function of the malaria vaccine?

   Probe: does your child still need a bed net? Why does the child still use a bed net or why not?

   Do you think people will behave differently if their child is vaccinated?

   Can your child still get malaria?

8. Was the malaria trial different from when you take your child to the clinic for other routine vaccines?

   Probe: If so, How?

EXPERIENCE WITH RESEARCH STUDY

9. What is your opinion on the way the vaccine is provided to your child?

10. What do you think it was like for your child to get the malaria vaccine?

    Prompt: how did they behave? Was your child comfortable?

Probe: Do the parents feel comfortable?

11. Do you think this malaria study was a good one?

    Prompt: things you liked or did not like.

    What encouraged you to participate?

    Could you ask questions if you didn't understand something?

    Did you understand the informed consent?

VACCINE UPTAKE

12. Do you think people in your community would get the vaccine if it becomes available in your community in the future?

    Probe: Do you think the malaria vaccine should be scaled up?

    Would people be willing to pay a little bit for it?

    Why only children under 5?

13. Do you like the idea of having something like this in the community?

    Probe: Why do you think only small children get it?

14. Is there anything else you think about this vaccine?

15. Is there anything else you would like to add or ask me?

Thank you for your time and help.

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

Ethical Implications of the Malaria Vaccine Development

Informed consent form researchers

Part I: Information Sheet

Introduction

I am Machteld van den Berg, a student at the Swiss Tropical and Public Health Institute. I am doing research that relates to ethical implications on malaria vaccine. I am going to give you information which will enable you make decision on whether to participate in this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

This consent form may contain words that you do not understand. Please ask me or stop as we go through the information and I will take time to explain. If you have questions later, you can ask them.

Purpose of the research

Malaria is a very common disease in this country and in sub-Saharan Africa which makes many people particularly children sick. Despite existing strategies to combat malaria in your community, we would

like to make further improvement and discourage disease transmission and associated deaths. We believe that you can help us doing this by telling us what you know both about malaria and about a vaccine that was tested against it. We want to learn what researchers think about how malaria vaccines are developed and how to improve the process.

Participant Selection

You are being invited to take part in this research because we think that your experience as a researcher can contribute much to our understanding and knowledge of malaria vaccine development.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. The choice that you make will have no bearing on your job or on any work-related evaluations or reports. You may change your mind later and stop participating even if you agreed earlier.

Research procedures

B. We are asking you to participate in research. If you accept, you will be asked to indicate your consent in the informed consent form. Thereafter you will take part in an interview with us which will take about one hour.

B. Interviews with myself and a local translator.

During the interview, we will sit down with you in a comfortable privacy place. If it is better for you, the interview can take place in your home or a friend's home. You will be requested to answer a series of questions during the interview. The interviewer will move from one question to the next question. There will be no wrong response. Every response will be valued. No one else but the interviewer will be present. The information recorded is confidential, and no one else except the project leader and research assistant will access the information documented during your interview. The entire interview will be tape-recorded based on your consent, but no-one will be identified by name on the tape. The tape will be kept secured in the office. The information

recorded is confidential, and no one else except the research assistant and myself will have access to the tapes. The tapes will be destroyed after 1 year.

Duration

We will conduct one interview and the interview will take about 1 hour.

Risks

There is a risk that you may share some personal or confidential information by chance, or that you may feel uncomfortable talking about some of the topics. However, we will ensure an intense confidential of information that you provide. You do not have to answer any question or take part in the interview if you feel the question(s) are too personal or if talking about them makes you uncomfortable. We will also try as much as possible not to make the interview long unnecessary.

Benefits

There will be no direct benefit to you, but your participation is likely to help us find out more about how to improve malaria prevention strategies in your community.

Confidentiality of Information

We will not be sharing information about you to anyone. The information that we collect from this research project will be kept private. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

Nothing that you tell us today will be shared with anybody outside the research team, and nothing will be attributed to you by name. The knowledge that we get from this research will be shared with you and your community before it is made widely available to the public. Following the meetings, we will publish the results so that other interested people may learn from the research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so, and choosing to participate will not affect your prospects as a researcher. You may stop participating in the interview at any time that you wish. I will give you an opportunity at the end of the interview to review your remarks, and you can ask to modify or remove portions of those, if you do not agree with my notes or if I did not understand you correctly.

Who to Contact

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact any of the following: Ms. Florence Were fachieng@kemricdc.org number 720 251 082; Machteld van den Berg, machteld.vandenberg@uzh.ch, +41 077 414 0594. If you have questions that relates to ethical issues you may contact the IHI-IRB administrator +254 703 034 375.

Part II: Certificate of Consent

I have been invited to participate in research about malaria and my experience as a researcher.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate [2]

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

- A one hour interview discussing malaria and my experience as a researcher

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability.

[2] A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb print as well.

I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Researcher interview guide

INTRODUCTION

My name is Machteld van den Berg and I am a student from Switzerland studying malaria. I am interested in learning more about your experience as researcher involved in RTS,S malaria vaccine phase III clinical trial.

Is it alright for you if I record the interview? No one except myself will have access to the recording and if you decide that you would like me to delete the recording, I will do this.

Is it alright for you to start the interview?

Questions

1. Can you describe the key activities around community engagement that took place during the RTS,S phase III?

2. What was your specific role and responsibility with engaging with the community in the Phase III study?

3. How did you feel when you were a part of those activities in the community?

What kinds of things caused joy and which caused conflict? Did anything make you feel uncomfortable?

4. What made certain activities more helpful than others?

Do you think there could be more exchanges? Or less?

5. What was the most important contribution of community participation?

6. What kinds of positive negative experiences did you have? Were they with specific groups in the study?

If so, how did you feel in those situations? Did you have the tools needed to deal with them?

7. Are there meaningful exchanges happening? In what ways were they helpful?

8. What kinds of questions did you have mothers asking about the study? Which questions were easy and difficult to answer?

9. In which situations did you feel the mother was not able to understand the study?

What did you do? What could have been done to facilitate understanding?

10.. What do you think can be done to improve further clinical research for malaria vaccines for the benefit of the community?

Curriculum Vitae

Machteld van den Berg

Born: 27. August 1989

Canadian and Dutch

EDUCATION

1994-1997	Primary Education, Theo Thijssen School, West-Knollendam, The Netherlands
1997-2004	Primary Education, Savanna School, Alberta, Canada
2004 - 2007	Secondary Education, Savanna School, Alberta, Canada
2007-2012	Bachelor of Science in Immunology and Infection (BSc), University of Alberta, Alberta, Canada
2013-2015	Master of Science in Infectious Disease, Drug Discovery and Vaccinology (MSc), Universities National Singapore (Singapore) and Basel, Switzerland
2016-2019	Doctoral Program in Biomedical Ethics (PhD), Institute of Biomedical Ethics and History of Medicine, University of Zurich, Switzerland

EMPLOYMENT HISTORY

07/2012-07/2013	Laboratory technician for the proteomics and immunoassay laboratory, *Roche Pharmaceuticals, Basel, University of Zurich*
03/2015-07/2015	Internship at *Gavi, the Vaccine Alliance in Geneva, Switzerland*
07/2015-11/2015	Consultant for monitoring and evaluations at *Gavi, the Vaccine Alliance,* in *Geneva, Switzerland*
01/2016-01/2017	Freelance Medical Writer for *NSPM in Meggen, Luzern, Switzerland*
01/2017-10/2018	Research Award Recipient to support program activities at the *International Development Research Centre, Ottawa, Ontario, Canada.*
02/2016-05/2019	Doctoral Researcher on vaccine development in low-resource settings, Advisors: Prof. Marcel Tanner and Prof. Nikola Biller-Andorno, *Institute of Biomedical Ethics and History of Medicine, University of Zurich*